Etiological and prognostic studies with the use of a population-based cancer registry

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Otto Visser

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1

INTRODUCTION

CANCER REGISTRY IN THE NETHERLANDS

Since 1989, the Netherlands has a nation-wide population-based cancer registry, the Netherlands Cancer Registry (NCR). Data collection for the NCR is organized by nine regional registries. Although in the Eindhoven region cancer registration already started in the 1950s, most Dutch cancer registries did not start their activities until the 1980s. The regional cancer registries in the Netherlands are hosted by the nine Comprehensive Cancer Centres (CCC) and together they completely cover the Netherlands. During the 1980s the CCCs made agreements with all hospitals in their regions to start cancer registration in the respective hospitals. This procedure was finalized during 1988 and on January 1st 1989 the cancer registry in the Netherlands reached national coverage. All regional registries submit their data to the NCR, which allows national analyses. Before accepting data from the regional registries in the NCR, the data are extensively checked for inconsistencies and duplicate records.
The collection of data for the regional cancer registries in the Netherlands is performed by registration clerks on the basis of data from the medical records of the cancer patients. As the registration clerks are trained and educated by the CCCs, and use national coding guidelines, data quality is high. New cancer cases are reported to the registration clerks by all pathology laboratories in the Netherlands on a weekly basis. Cancer cases who were not microscopically confirmed are reported annually by the national hospital discharge registry. With these two notification sources the completeness of the NCR is at least 95%.
In 1997, the data of the NCR covering 1989-1992 were accepted by the International Association of Cancer Registries (IACR) for publication in Volume VII Cancer Incidence in Five Continents[1]. Five years later, the data covering 1993-1997 were included in Volume VIII of Cancer Incidence in Five Continents[2]. In addition to the minimum data set of the IACR (date of birth/age, sex, date and basis of diagnosis, site and morphological type of the tumour), the regional registries collect stage data for all relevant tumours, as well as data on primary treatment. The treatment data increase the possibilities for use of the regional cancer registries substantially, but they are not (yet) included in the national database.

THE AMSTERDAM CANCER REGISTRY

The Amsterdam Cancer Registry (ACR), the cancer registry of the Comprehensive Cancer Centre Amsterdam (CCCA), started its activities in 1984 in Medisch Centrum Alkmaar, the largest community hospital of the CCCA. In the following years, the ACR gradually expanded by the inclusion of more hospitals. In 1988, the ACR reached region-wide coverage. Due to mergers and closing of several small hospitals, the number of hospitals of the CCCA gradually decreased from over 30 during the 1980s to 20 in the second half

Figure 1.
The region of the Amsterdam Cancer Registry

of the 1990s. Subsequently, the number of hospitals has been stable, but the hospitals who have two or three locations following a merger, tend to centralize their activities at one location. Among the hospitals which participate in the ACR are two university hospitals and a specialized cancer hospital, all located in Amsterdam. These three hospitals are the ones with radiotherapy facilities. As of 1996, radiotherapy facilities are also available in one of the community hospitals.

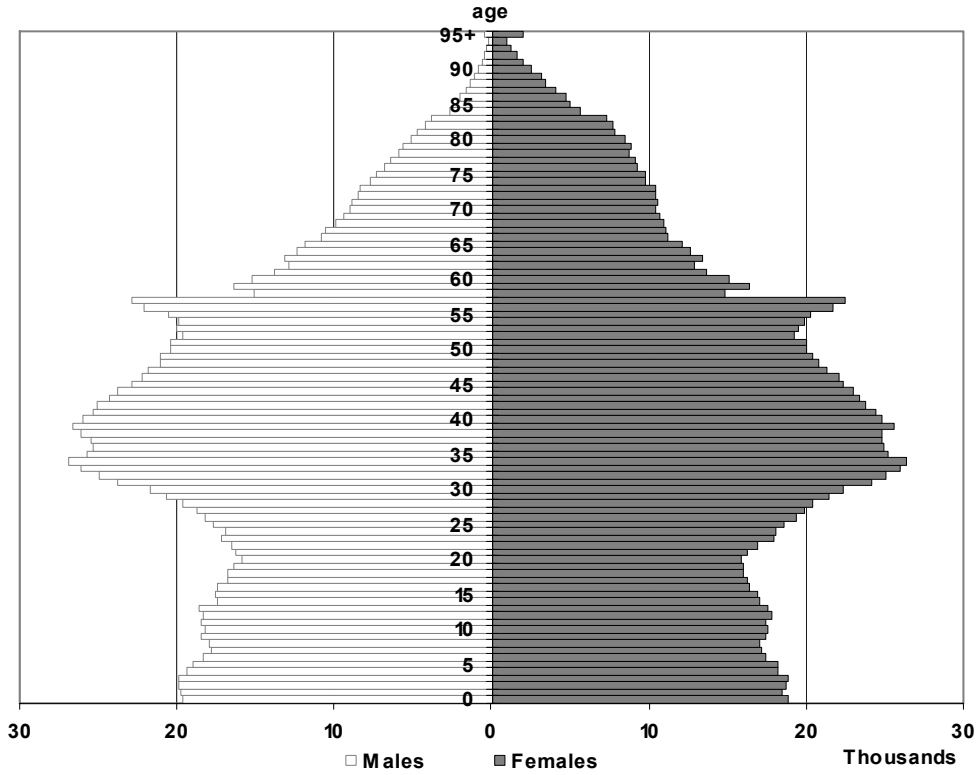

Figure 2. Population pyramid of North-Holland/Flevoland, 1-1-2004

The region of the CCCA and the ACR comprises the province of North-Holland as well as the major part of the province of Flevoland. Due to the merger of two hospitals in Flevoland, the remaining part of Flevoland will be included in the near future. The ACR is the largest of the nine regional cancer registries in the Netherlands and covers a population of 2.885 million on January 1st 2004, which is about 18% of the total population of the Netherlands. As figure 2 shows, the proportion of elderly people is still relatively small. Since 1988, the proportion of people of 65 years or older has been stable at 13 percent. However, the proportion of people of 85 years or older gradually increased from 1.2 to 1.4 percent. As of 2008, when he first 'baby-boomers'* reach

* The 'baby-boom' started in the Netherlands in 1943, when the number of births increased 10% in comparison to 1942 and exceeded 200 000 for the first time in history, and came to an end 30 years later in 1973, when the number of births decreased below 200 000 again. The average annual number of births during the 'baby-boom' was 237 000, compared to 175 000 in the decades before and 187 000 in the decades after the 'baby-boom'.

the age of 65 years, the proportion of people of 65 years will gradually increase. This demographic development will increase the cancer burden during the next decades substantially, as cancer is most common among the elderly[3].
The number of migrants in North-Holland and Flevoland gradually increased during the past decades. On 1-1-2004, the proportion of first generation migrants was 14% (national figure: 10%), while 12% were second generation migrants[4]. In Amsterdam, even more than half of the population is a first or second generation migrant. Migrants originate primarily from the former Dutch colonies (Indonesia [former name: Dutch East-Indies], Surinam and the Netherlands Antilles), Morocco and Turkey. Migrants from the latter two countries originally came to the Netherlands as labour migrants in the 1960s, but the vast majority came to the Netherlands as part of family reunion or marriage. During the 1990s, a new category of migrants emerged, namely asylum seekers. These originate primarily from the former Yugoslavia, Iraq, Iran, Afghanistan and Somalia. However, their numbers are relatively small in comparison to the 'traditional' migrants.

CANCER INCIDENCE, MORTALITY AND PREVALENCE IN NORTH-HOLLAND & FLEVOLAND

Incidence of invasive cancers in North-Holland/Flevoland

In 1988, 9 532 invasive cancer cases were diagnosed in residents of the region of the ACR (table 1). In 2002, this number had increased to 11 987, an increase of 26%. However, this increase was mainly caused by growth of the population. The age-standardized incidence rate per 100 000 persons only increased by 3% (both sexes combined). Until the year 2000, the number of cancer cases in males exceeded the number in females. Since then, more females were diagnosed with cancer than males. The fast increase in the number of diagnosed cancers in females during the beginning of the 1990s is mostly due to the introduction of the breast cancer screening, which has led to an increase of the number of breast cancers of about 50% (or 700 cases) between 1988/89 and 2001/02. The number of lung cancers in females doubled between 1988 and 2002 (from 250 to 500 cases).

Table 1. Incidence of cancer in North-Holland/Flevoland

Year of diagnosis	*Number of cases per year*		
	both sexes combined	*males*	*females*
1988	9 532	4 990	4 542
1989	9 711	5 004	4 707
1990	10 275	5 413	4 862
1991	10 317	5 378	4 939
1992	10 776	5 590	5 186
1993	10 858	5 598	5 260
1994	11 130	5 684	5 446
1995	11 313	5 839	5 474
1996	11 365	5 851	5 514
1997	11 492	5 910	5 582
1998	11 522	5 852	5 670
1999	11 597	5 938	5 659
2000	11 791	5 922	5 869
2001	12 066	6 008	6 058
2002	11 987	5 986	6 001

The crude incidence rate per 100 000 (figure 3) gradually increased in females and almost equalled the crude rate in males in 2001/2002. The crude rate in males has

been rather stable during the last decade. The age-standardised incidence rate* for both sexes combined increased from 377 per 100 000 in 1988 to 409 in 1995. Subsequently, the rate decreased to 389 per 100 000 in 2002. Throughout the whole period the incidence rate in males was higher than in females, but the difference decreased from 131 per 100 000 in 1988 to only 72 in 2002 (the male/female ratio decreased from 1.4 in 1988 to 1.2 in 2002).

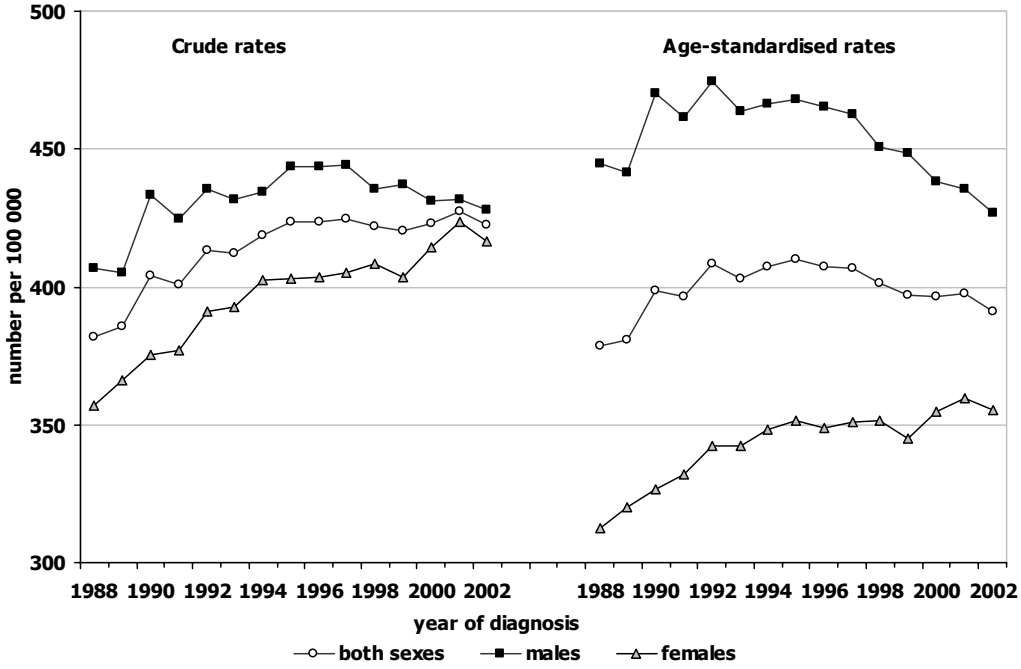

Figure 3. Cancer incidence rates in North-Holland/Flevoland, 1988-2002

Cancers of the breast, lung, colon & rectum and prostate account for 50% of all cancers (table 2). In 1988, lung cancer was the most common cancer, but as of 1991, breast cancer is the most common cancer. Colorectal cancer ranks third, and prostate cancer fourth (7.3% in 1988, 9.6% in 2002). The proportion of skin cancer† increased between 1988 and 2002, while the proportion of stomach cancer decreased (4.8% in 1988, 2.6% in 2002). In 3% to 4% of all registered cases, the primary site of the cancer is unknown. In males, lung cancer and prostate cancer changed position between 1988 and 2002 (table 3), while colorectal cancer remained the third cancer in males. Due to the increase in oesophageal cancer incidence, this cancer, which was not among the most frequent cancers in the 1990s, became the 10th cancer in males in 2002. In females, breast cancer is by far the most common cancer and its proportion even increased between 1988 and 2002 from 29% to 33%. The proportion of cancers of the female genital organs decreased between 1988 and 2002 (cervix uteri from

* European standardised rate (ESR), i.e. standardised according to the European standard population

† Excluding basal cell carcinoma (the most common type of skin cancer), which is not registered by the ACR

3.4% to 2.1%, corpus uteri from 4.9% to 4.0%, ovary from 4.3% to 3.3%), while the proportion of skin and lung cancer increased.

Table 2. The ten most frequent cancer sites in North-Holland/Flevoland (both sexes combined)

1988			*2002*		
site	*n*	*%*	*site*	*n*	*%*
Lung	1 448	15.1	Breast	2 035	16.4
Breast	1 350	14.1	Lung	1 603	12.9
Colon & rectum	1 163	12.2	Colon & rectum	1 575	12.7
Prostate	698	7.3	Prostate	1 190	9.6
Skin*	597	6.2	Skin*	1 067	8.6
- melanoma		3.1	- melanoma		4.0
- other skin cancers*		3.2	- other skin cancers*		4.6
Stomach	458	4.8	Lymphatic tissues†	500	4.0
Lymphatic tissues*	411	4.3	Bladder & oth. ur. tract	451	3.6
Bladder & oth. ur. tract	400	4.2	Head & neck	423	3.4
Uterus	382	4.0	Uterus	378	3.1
- cervix		1.6	- cervix		1.1
- corpus		2.3	- corpus		2.0
Head & neck	322	3.4	Stomach	328	2.6

Table 3. The ten most frequent cancer sites in males in North-Holland/Flevoland

1988			*2002*		
site	*n*	*%*	*site*	*n*	**%**
Lung	1 200	24.0	Prostate	1 190	19.2
Prostate	698	14.0	Lung	1 073	17.3
Colon & rectum	550	11.0	Colon & rectum	813	13.1
Skin†	307	6.1	Skin*	530	8.5
- melanoma		2.5	- melanoma		3.2
- other skin cancers*		3.6	- other skin cancers*		5.4
Bladder & oth. ur. tract	298	6.0	Bladder & oth. ur. tract	344	5.5
Stomach	286	5.7	Head & neck	289	4.7
Lymphatic tissues‡	233	4.7	Lymphatic tissues†	283	4.6
Head & neck	224	4.5	Stomach	192	3.1
Pancreas	139	2.8	Bone marrow‡	176	2.8
Bone marrow§	133	2.7	Oesophagus	168	2.7

Second cancers

Second and subsequent cancers are not uncommon. Of all registered invasive cancers in 1988 7 percent was not the first cancer if the IACR-rules for multiple cancer were applied to the data[5]. This percentage increased to more than 10 percent in 2002. Among the second and subsequent cancers, colorectal cancer, lung cancer, non-melanoma skin cancer and urinary tract cancers are relatively common. As the NCR also registers contralateral cancers (mainly breast cancer) and multiple cancers of the colon, the proportion of second or subsequent cancers is 2 percent higher if these cancers are also included.

* Lymphoma
† Excluding basal cell carcinoma (the most common type of skin cancer), which is not registered by the ACR
‡ Lymphoma
§ Leukaemia

Table 4. The ten most frequent cancer sites in females in North-Holland/Flevoland

1988			*2002*		
site	*n*	*%*	*site*	*n*	*%*
Breast	1 337	29.3	Breast	2 024	32.8
Colon & rectum	613	13.4	Colon & rectum	762	12.3
Uterus	382	8.4	Skin*	537	8.7
- cervix		3.4	- melanoma		4.8
- corpus		4.9	- other skin cancer*		3.9
Skin*	290	6.4	Lung	530	8.6
- melanoma		3.7			
- other skin cancers*		2.6			
Lung	248	5.4	Uterus	378	6.1
			- cervix		2.1
			- corpus		4.0
Ovary	197	4.3	Lymphatic tissues†	216	3.5
Lymphatic tissues†	178	3.9	Ovary	205	3.3
Stomach	172	3.8	Stomach	136	2.2
Pancreas	126	2.8	Head & neck	134	2.2
Bladder & oth. ur. tract	102	2.2	Bone marrow‡	133	2.2

Mortality due to cancer in North-Holland/Flevoland

Table 5. Mortality due to cancer in North-Holland/Flevoland

Year of diagnosis	*Number of deaths per year*		
	both sexes combined	*males*	*females*
1988	6 161	3 456	2 705
1989	6 114	3 388	2 726
1990	6 189	3 380	2 809
1991	6 118	3 333	2 785
1992	6 177	3 389	2 788
1993	6 165	3 339	2 826
1994	6 227	3 374	2 853
1995	6 176	3 375	2 801
1996	6 257	3 361	2 896
1997	6 229	3 291	2 938
1998	6 257	3 408	2 849
1999	6 290	3 393	2 897
2000	6 317	3 352	2 965
2001	6 235	3 252	2 983
2002	6 435	3 427	3 008

In males, the annual number of cancer deaths was rather stable during the period 1988-2002. In females, there was a 10% increase in the number of cancer deaths (table 5). The age-standardised mortality rate per 100 000 persons decreased from 240 in 1988 tot 202 in 2002, a decrease of 16% (figure 4). This decrease was mostly due to the decrease in males: from 312 in 1988 to 245 in 2002 (-22%). In females the decrease of the age-standardised rate was 5%. In males, the decrease in cancer mortality was caused by a decrease in the mortality due to lung cancer (-36%), stomach cancer (-48%) and prostate cancer (-26%). In females, there were decreases in the mortality due to breast cancer (-15%) and ovarian cancer (-29%), but the mortality due to lung cancer increased by 161%.

Cancer prevalence in North-Holland/Flevoland

On January 1st 2003, 61 100 persons in whom cancer had been diagnosed in North-Holland/Flevoland since December 31st, 1987 were still alive (table 6). This number is the 15-year cancer prevalence. The total cancer prevalence is even higher, because there are also people still alive in whom cancer was diagnosed before 1988, the start of the ACR.

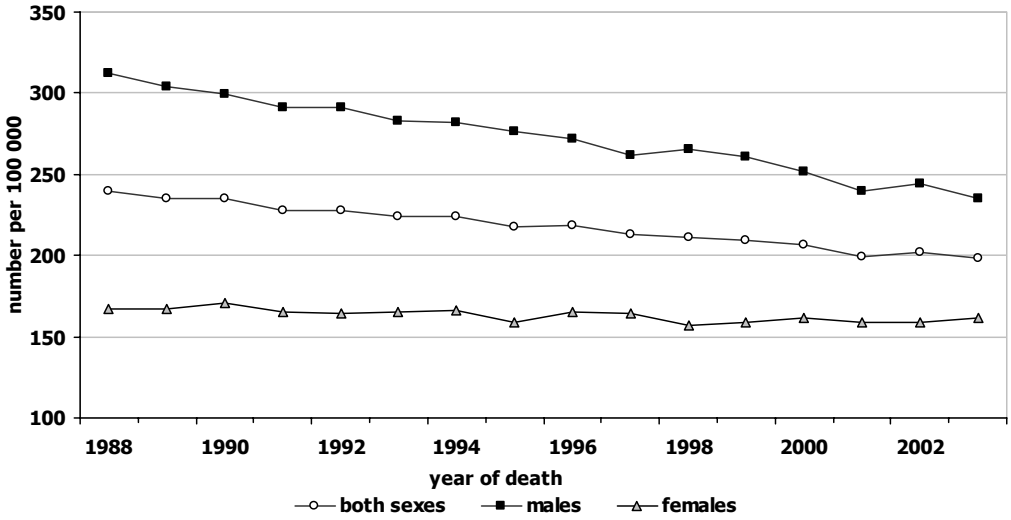

Figure 4. Age-standardised cancer mortality rates in North-Holland/Flevoland, 1988-2003

Table 6. The ten most prevalent cancer sites in North-Holland/Flevoland (both sexes combined), January 1st 2003 (15-year cancer prevalence)

site	*number*	*ESR*
1. Breast	16 300	497
2. Skin*	7 700	240
- melanoma	4 300	137
- other skin cancers*	3 400	103
3. Colon/rectum	7 500	230
4. Prostate	6 600	235
5. Uterus	3 350	99
- cervix	1 950	56
- corpus	1 400	43
6. Lymphatic tissues	2 850	93
7. Lung	2 500	85
8. Head & neck	2 500	83
- larynx	800	28
- oral cavity	700	23
9. Bladder/other urinary tract	2 100	70
10. Kidney	1 250	40
All sites	61 100	1 947

This includes mostly individuals who were cured from breast cancer, colorectal cancer, cervical cancer, skin melanoma, testicular cancer or Hodgkin's disease. Cancer prevalence is an important measure of the occurrence of cancer, since it provides information on the total number of patients with need for care. Such information is crucial for health care planning. The age-standardised 15-year prevalence per 100000 persons was 1947 (males 1796, females 2099). Breast cancer, skin cancer and colorectal cancer have the highest prevalence. Cancer prevalence comprises a heterogeneous group of (ex-)patients, who may have completely different needs for care. The following phases, each with its specific need for care, may be distinguished[6]:

- diagnostic phase
- treatment phase
- disease-free phase
- palliative or terminal phase
- cured phase

The longer the length of the prevalence period, the more heterogeneous the cancer prevalence is. The 1-year prevalence comprises mostly patients in the diagnostic and treatment phase. One to five years after diagnosis the majority of the patients is either disease-free or develops a recurrence and reaches the terminal phase. The majority of the patients who survive the first 5 years are cured. In general, the longer the length of the prevalence period, the higher the proportion of cured patients is. Therefore, when a relation with the need for care is requested, it is better to choose a prevalence period which does not exceed for example 10 or 15 years. Only for long-term survivors who are at risk for second cancers and other late treatment-related effects, a longer prevalence period might be informative.

FOLLOW-UP OF CANCER PATIENTS

In order to be able to determine cancer survival rates, complete follow-up of the registered cancer cases is essential. However, the follow-up of cancer patients is one of the most difficult tasks of a cancer registry. Follow-up may include the following items:

- occurrence of local and/or regional recurrence
- occurrence of distant metastasis
- vital status and the date of death
- cause of death

The collection of information on the first two items requires access to the medical record. Although the ACR has access to the patients' records, the collection of follow-up data is time-consuming and therefore the ACR only collects such data in registration studies for a limited number of cancers over a limited period. An example of such a registration study is discussed in chapter 4.4.
For the vital status and the date of death the following main sources are available in the Netherlands:

1. the hospital where the tumour was registered
2. the general practitioner
3. the municipal population registers
4. the Central Bureau of Genealogy (CBG)

For this thesis, the general practitioner was only incidentally used as the source of follow-up information. We performed the following procedure for obtaining complete vital status and date of death information. For patients with residence in the ACR region and diagnosed in 1988-97, the vital status was updated by linking electronic files with deceased persons to the cancer registry. These files were made available in 1999/2000 by 54 municipal population registers (covering 90% of the population of the region) out of a total of 74 registers in the region. The files included all deceased residents (irrespective of cause of death) of those municipalities, generally covering the period 1988-99. Active follow-up was performed in the hospitals for all patients with residence in the remaining 20 municipalities and in case the datafile made available by the municipal population register only partly covered the period 1988-99. In case of missing data in the hospital, the municipal population registers were asked for the date of death of individual patients.
In September 2003, the vital status of all patients (diagnosed 1988-2001) still alive at last follow-up was updated by linkage to the electronic death register of the CBG,

which contains all deceased residents of the Netherlands as of October 1st 1994. This electronic register is updated on a daily basis with data from all municipal population registers in the Netherlands. Patients who probably died before October 1st 1994 according to hospital information, but with unknown date of death, were checked in the personal record card register of the CBG which contains all Dutch residents who died before October 1st 1994. Finally, all patients not known by CBG were assumed to be alive at 1 September 2003, one week before record linkage with the electronic death register was performed.
Checks on the vital status of patients assumed to be alive at 1 September 2003 were performed in the hospitals for all patients with metastatic disease at diagnosis, patients over 95 years of age in 2003 and patients with cancer of the oesophagus, stomach, liver, gallbladder, bile ducts, pancreas, and lung. These hospital checks revealed that the number of patients who were assumed to be alive after record-linkage but appeared to have died, was negligible. Missing dates of death are estimated to be well below 0.5%.
As neither the municipal population registers nor the CBG possess information regarding the cause of death and the collection of the cause of death in hospitals and from general practitioners is extremely time-consuming, information on the cause of death is absent for the majority of the cases and could not be used in survival analysis. Although the individual causes of death are available at Statistics Netherlands, this information was hardly accessible for cancer registries because of strict privacy regulations, and could not be used in this thesis.
In the studies of chapter 4 follow-up data were used for the calculation of survival probabilities, local recurrence rates and hazard ratios for the risk of dying.

CANCER SURVIVAL IN NORTH-HOLLAND & FLEVOLAND

As an alternative to disease-specific survival, we calculated relative survival with software written by Dickman et al[7], based on a computer package developed by Hakulinen et al[8]. This method corrects observed survival for expected mortality according to annual life tables of the general population. We used national age-, sex- and calendar year-specific life tables from Statistics Netherlands[9].
As shown in figure 5, there is a large variation in cancer survival by site of the tumour. Cancers with the highest survival rates are skin cancer (including melanoma) and testicular cancer. Breast cancer, prostate cancer, Hodgkin lymphoma and thyroid cancer also have a fairly good prognosis. Cancer of the digestive organs (colorectal cancer excluded), lung cancer, mesothelioma and brain cancer have the worst survival rates. The most important prognostic factor for survival is stage and many differences in survival probabilities between cancer sites can be attributed to differences in stage distribution. This will be discussed extensively in chapter 4.1 of this thesis.
For several cancers, such as colorectal cancer, cancer of the cervix & uterine corpus and primary bone cancer, the 5-year relative survival rate (RSR) is almost equal to the 10-year RSR. However, for other cancer sites, such as breast cancer, prostate cancer and haematological malignancies there is still substantial excess mortality between 5 and 10 years after diagnosis in comparison to the general population.

During 1988-2001, survival slightly improved for all cancer sites combined. This was due to improved survival of some common cancers (breast cancer, colorectal cancer, prostate cancer) as well as changes in cancer incidence: the proportion of several cancers with poor survival (lung cancer, stomach cancer) has decreased between 1988 and 2001, while the proportion of cancers with a relatively favourable prognosis (breast cancer, prostate cancer, skin cancer) has increased.

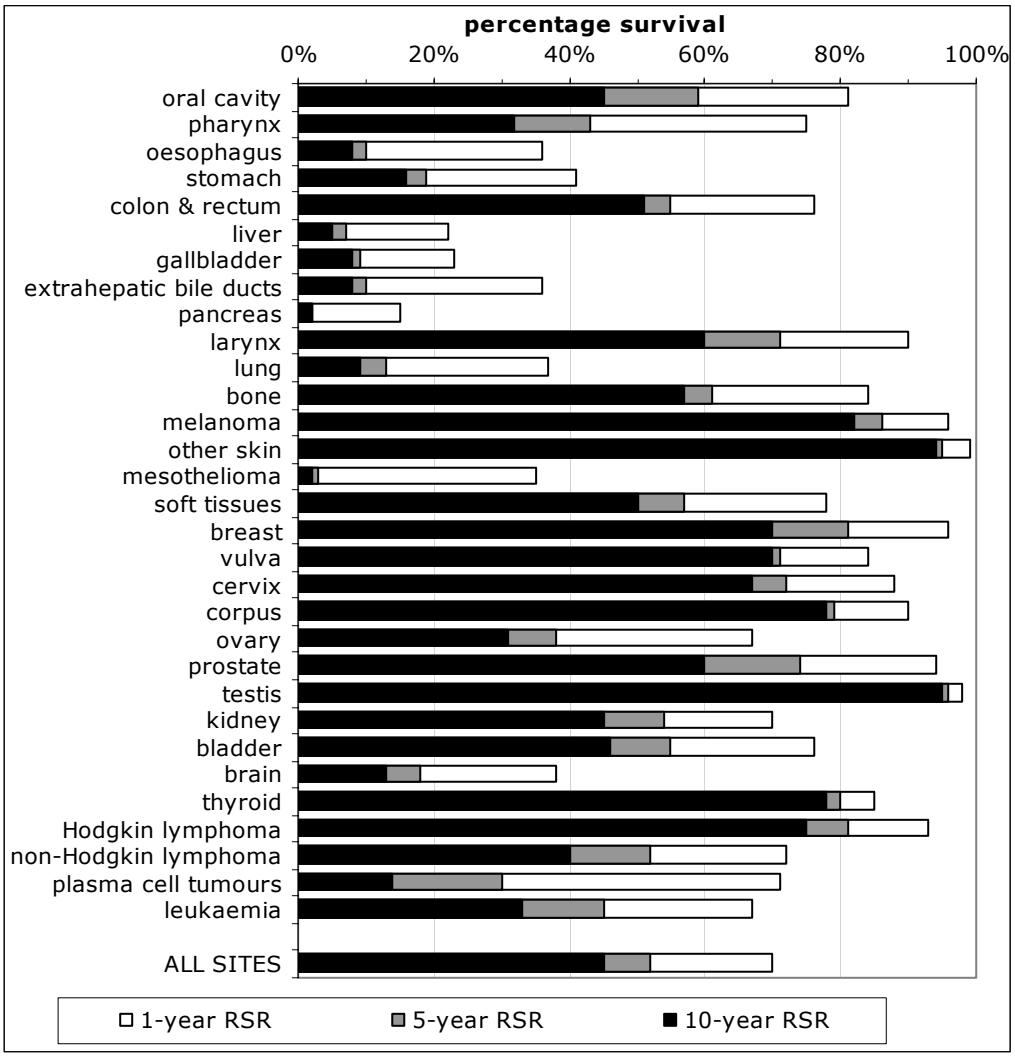

Figure 5. Relative survival rate (RSR) by cancer site, North-Holland & Flevoland, 1988-2001

STUDIES WITH A POPULATION-BASED CANCER REGISTRY

Apart from the obvious way to use a cancer registry for the calculation of cancer incidence rates, there are numerous possibilities for research with population-based can-

cer registries, ranging from descriptive epidemiological studies and health care planning to aetiological and clinical research. In this thesis, the various uses of a population-based cancer registry are illustrated by migrant studies, studies of the association between environmental factors and the occurrence of cancer, and research on prognosis and survival of cancer patients. Below, the various types of research are briefly discussed.

Descriptive epidemiology

A population-based cancer registry enables the description of cancer patterns in relation to characteristics such as age, sex, residency, year of diagnosis and country of birth. This information is valuable for medical specialists and health authorities, may assist in the planning of (new) health care services and may also provide clues for the aetiology of cancer and hypotheses for further research. The migrant studies in **chapter 2** are examples of descriptive epidemiology. For these studies, information about the country of birth was essential. Although this item is routinely collected by the Netherlands Cancer Registry, the country of birth is often unknown in the hospitals and the available data were supplemented with information from the breast cancer screening organisation and several other sources.
The research questions for the migrant studies were:

- Are there differences in breast cancer risk between migrant women from non-western countries in comparison to women born in the Netherlands?
- Are there differences in cervical cancer risk between migrant women from non-western countries in comparison to women born in the Netherlands?

The research questions with regard to breast cancer screening were also aimed mainly at migrant women (see 'evaluation of screening programmes').

Aetiological research

Descriptive studies can provide interesting clues to cancer aetiology, but in-depth studies are required to test the proposed hypotheses. In an ecological (or correlation) study design groups of individuals are the subject of study (and unit of analysis) and a comparison is made between these groups.[10] In many ecological studies, the disease data and the exposure data are routinely collected. In order to investigate possible associations a comparison is made between two ore more populations, often based on geographical entities (geographical correlation study) or by comparing different time periods. A combination of geographical entities and time periods is also possible. A major deficiency of ecological studies is the use of aggregated data instead of individual data and, hence, the interpretation of the outcome of ecological studies is difficult. By contrast, in analytical study designs, such as cohort or case-control studies, data of individuals are used. For prospective or retrospective cohort studies, it is possible to link data files which include exposure data of participating individuals with the cancer registry. Since the start of the NCR in 1989, two large prospective cohort studies[11,12] and several smaller studies have made use of this possibility. In case-control studies, which compare cancer patients with disease-free controls, detailed data on life style factors are needed. Such data are not available in the cancer registry, but the cancer

registry is a powerful, unbiased (population-based) tool for the selection of patients eligible for a case-control study.[13]
In **chapter 3**, two ecological studies which investigated the relation between air pollution and cancer risk are presented. Both studies are based on the address of the patient at diagnosis. In the study regarding the incidence of cancer in the area around Schiphol, no individual information regarding exposure to air pollution was available and we use an ecological study design.
In the study which investigated the relation between air pollution and residency along the main roads in Amsterdam, individual information regarding the exposure to main road traffic was available. Traffic intensity (with separate data for trucks and cars) for all separate segments of the main road network was used as a measure for traffic-related air pollution. This information enabled a comparison between heavily exposed and less exposed residents of Amsterdam in a study with a cohort-design. Because the standard address information in the cancer registry was insufficient to answer the research question, supplementary address data were used from the population registry of Amsterdam. The exposure data (traffic density on the main roads) were subsequently linked to the individual cancer patients.
The following research questions were studied:

- Is there an association between residency in the Schiphol area and the risk to develop cancer?
- Is there an association between residency along the main roads of Amsterdam and the risk to develop cancer and does the risk of specific cancers increase with exposure to higher levels of air pollution as assessed by residency along roads with the highest traffic density?

Clinical research

The effect of various treatments on cancer recurrence and survival can best be studied in randomised clinical trials. However, a major drawback of clinical trials is that they are always performed in selected patient populations which are often healthier than the general population. By using a population-based cancer registry, the effects of changes in treatment modalities on recurrence and survival rates can be studied in an unselected population. In **chapter 4** the results of four prognostic, registry-based studies are presented. For three studies we used standard information, as available in the cancer registry. For the bladder cancer study, supplementary information on the occurrence of local recurrence was collected.
The following research questions were studied in chapter 4:

- To what extent does TNM-stage at diagnosis influence survival in patients with epithelial cancers (chapter 4.1)?
- Has stage-specific survival changed over time (chapter 4.1)?
- What are the survival rates of carcinoid tumours and has an in improvement of the survival of metastatic carcinoid disease occurred after the introduction (in 1992) of octreotide into clinical practice (chapter 4.2)?
- What has been the effect of population-based cervical cancer screening on the incidence and survival of cervical cancer (chapter 4.3)?
- What is the risk of local recurrence after cystectomy for bladder cancer and what is the prognosis after recurrence (chapter 4.4)?

Evaluation of screening programmes

A population-based cancer registry plays an important role in the evaluation of screening programmes. For example, although ultimately the effect of the breast cancer screening programme can be evaluated by monitoring the mortality due to breast cancer, the cancer registry additionally offers the possibility to monitor trends in cancer incidence, stage distribution, treatment practices in screen-detected versus non-screen-detected cases. The cancer registry can also supply information on interval carcinomas. The study in chapter 2.3 regarding the screening results in migrant women is an example of supplementary information that can be offered by the cancer registry. In collaboration with the breast screening organisation, the following researched questions were studied with data from the regional breast cancer screening program:

- What are the attendance rates of migrant women from non-western countries in the screening programmes for breast cancer?
- What are the results of the screening for those women who did attend the breast cancer screening?

The study in chapter 4.3 regarding incidence and survival of cervical cancer also investigated the effect of the cervical cancer screening programme.

Pattern of care studies

Finally, a population-based cancer registry is an excellent tool for the study of cancer care, for example for the study of the use of guidelines or the study of determinants of the care process. As no pattern of care studies are presented in this thesis, prospects for future use of the cancer registry for this purpose will be discussed in **chapter 5**. The results of the presented studies in this thesis will also be discussed in chapter 5.

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Amiano P, Navarro C, Quiros JR, Key TJ, Allen N, Khaw KT, Bingham SA, Psaltopoulou T, Koliva M, Trichopoulou A, Nagel G, Linseisen J, Boeing H, Berglund G, Wirfalt E, Hallmans G, Lenner P, Overvad K, Tjonneland A, Olsen A, Lund E, Engeset D, Alsaker E, Norat T, Kaaks R, Slimani N, Riboli E. Consumption of vegetables and fruits and risk of breast cancer. JAMA. 2005;293:183-93.

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2

MIGRANTS AND CANCER

2.1 Incidence of cervical cancer in women in North-Holland by country of birth, 1988-1998

Visser O, Busquet EH, van Leeuwen FE, Aaronson NK, Ory FG. [Incidence of cervical cancer in women in North-Holland by country of birth from 1988-1998]
Ned Tijdschr Geneeskd. 2003 Jan 11;147(2):70-4

ABSTRACT

Objective
To describe the incidence of cervical cancer in North-Holland by country of birth.
Design
Descriptive epidemiological study based on data from cancer registries.
Method
The number of cases of cervical cancer in North-Holland for the period 1988-1998 was determined on the basis of data available from the regional cancer registry of the Comprehensive Cancer Centre Amsterdam. Based on data from the Netherlands Cancer Registry, a comparison was made between the observed and the expected number of cases by area of residence (i.e., Amsterdam versus the rest of North-Holland) and by country of birth.
Results
In the period 1988-1998, the incidence of cervical cancer among women living in North-Holland was significantly higher than that of the nation as a whole (O/E-ratio 1.2; 95% CI 1.1-1.2). In particular, the incidence of cervical cancer for women living in Amsterdam (O/E-ratio 1.5; 95% CI 1.4-1.6), and for women born in Morocco (O/E-ratio 2.1 95% CI 1.4-3.1) or Surinam (O/E-ratio 1.5 95%CI 1.1-2.0) was much higher. The percentage of patients with higher stages (TNM-stages II-IV) did not differ between women born in the Netherlands and those born abroad.
Conclusion
The incidence of cervical cancer during the period 1988-1998 was significantly higher for women living in Amsterdam and for women born in Morocco or Surinam than that for the Netherlands as a whole. No significant difference in stage of disease at diagnosis was observed between women born in the Netherlands versus those born abroad.

INTRODUCTION

In the Netherlands, about 700 cases of cervical cancer are diagnosed annually, 2.5% of all newly diagnosed malignancies in females. The age standardised incidence rate (world standardised rate: WSR) was 6.5 per 100 000 women in 1997 (1).
Large worldwide variation exists in the incidence of cervical cancer. In Latin America the incidence is very high, while it is low in Israel (2). Moreover, differences have been found between immigrants or ethnic minorities and the local population, i.e. in England & Wales (3), the Unites States (National Cancer Institute. Cervix Uteri Cancer. US Racial/Ethnic Cancer Patterns. www.cancer.gov/cancerinfo/doc.aspx?viewid=1c763de8-c2ef-4501-b440-09e836342fe9) and Israel (2). During the past decades many migrants from high incidence areas have settled in the Netherlands, especially in the major cities. Nevertheless, the incidence of squamous cell carcinoma of the cervix decreased during 1989-1997 (1). There was also a decrease in Amsterdam.
For some time, screening programmes for cervical cancer have been in operation in the Netherlands. The attendance was unsatisfactory and consequently in 1996, a new programme was introduced. This new programme aims at an attendance of at least 60%, but in several migrant groups this percentage is not met (4,5). In this study, we investigated differences in the incidence of cervical cancer among women born in the Netherlands and foreign-born women to be able – if necessary- to aim extra information activities at groups with an increased cervical cancer risk.

METHODS

Since 1988, cancer patients are registered in all hospitals in the region of the Comprehensive Cancer Centre Amsterdam (CCCA): this region covers the province North-Holland and the major part of Flevoland. All information is extracted from the medical records by trained registration clerks. Apart from demographic items, which includes the place of birth or – if a patient was born outside the Netherlands – the country of birth, information on the type of cancer and the primary treatment are registered. For the year 1988, stage was classified according to the Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) (6) and for 1989-1998 according to the 4th edition of the TNM-classification (6).
For this study all women with residence in North-Holland and invasive cervical cancer diagnosed between 1 January 1988 and 31 December 1998 were selected. If women with residence in North-Holland were registered in a hospital outside the region, the data from the nation registry were used.

Definition migrants

In this study a migrant was defined as a Dutch resident who was born outside the Netherlands.

Population data

Starting from 1995, Statistics Netherlands published annual population data for North-Holland and Amsterdam of persons born in Turkey, Morocco, Surinam, Indonesia or the Netherlands Antilles/Aruba (considered as one country). For the preceding years

population data for 1992 (5 countries) and 1989-1994 (Surinam and Netherlands Antilles/Aruba) were supplemented with extrapolations for the remaining years, using also data according to nationality. Separate data for persons born in the Netherlands were not available.

Statistical analysis

Incidence rates were calculated as WSR. The WSR uses the world standard population for age standardisation (7).
Using the population data (according to age group) and incidence data from the Netherlands Cancer Registry for 1989-1997 we calculated expected numbers of cervical cancer in North-Holland (E) for the period 1988-1998 (1). The numbers were compared with the observed numbers (O) and O/E-ratios were calculated. Exact 95% confidence intervals (95% CI) based on the Poisson distribution were calculated with Stata 6.0 (8).

RESULTS

In North-Holland, 1530 women with cervical cancer were registered in the period 1988-1998 (table 1).

Table 1. Number of women (%) with cervical cancer in North-Holland, 1988-1998

	total	with residence in	
		Amsterdam	other North-Holland
total	1530	572	958
age			
0-29 years	89 (6)	32 (6)	57 (6)
30-59 years	937 (61)	338 (59)	599 (63)
60 years or older	504 (33)	202 (35)	303 (32)
country of birth			
Netherlands	1138 (74)	386 (67)	752 (78)
abroad	232 (15)	143 (25)	89 (9)
Turkey	16 (1)	10 (2)	6 (1)
Morocco	26 (2)	22 (4)	4 (0)
Surinam	50 (3)	44 (8)	6 (1)
Ned. Antilles/Aruba	7 (0)	4 (1)	3 (0)
Indonesia	30 (2)	7 (1)	23 (2)
other	103 (7)	56 (10)	47 (5)
unknown	160 (10)	43 (8)	117 (12)
TNM-stage at diagnosis (FIGO-classification)			
I	774 (51)	275 (48)	499 (52)
II	286 (19)	95 (17)	191 (20)
III	323 (21)	143 (25)	180 (19)
IV	102 (7)	41 (7)	61 (6)
unknown or not applicable	45 (3)	18 (3)	27 (3)

FIGO = Fédération Internationale de Gynécologie et d'Obstétrique

About 6% was below the age of 30 years, something over 60% was between 30 and 60 years old, while one third was 60 years or older. Of the total of 1530 women, 1138 (74%) were born in the Netherlands and 232 (15%) were born abroad. The country of birth could not be retrieved for 160 women (10%). The percentage of foreign born women in Amsterdam (25%) was 2.5 times as high as in the remaining part of North-Holland (9%). In Amsterdam, the number of women born in Surinam and Morocco was relatively high.

Table 2. Age standardised incidence of cervical cancer per 100 000 women per year in North-Holland according to country of birth and in the country of origin, 1988-1998* (9)

country of birth	in North-Holland	in country of origin[9]
Turkey	10.5	4.5 5.4 (Izmir 1993-94) [10]
Morocco	15.3	19.5
Surinam	12.9	33.4
Netherlands Antilles/Aruba	6.1	20.4 [11]
Indonesia	6.3	15.9

* The total age standardised incidence in North-Holland was 8.2 per 100 000 women per year

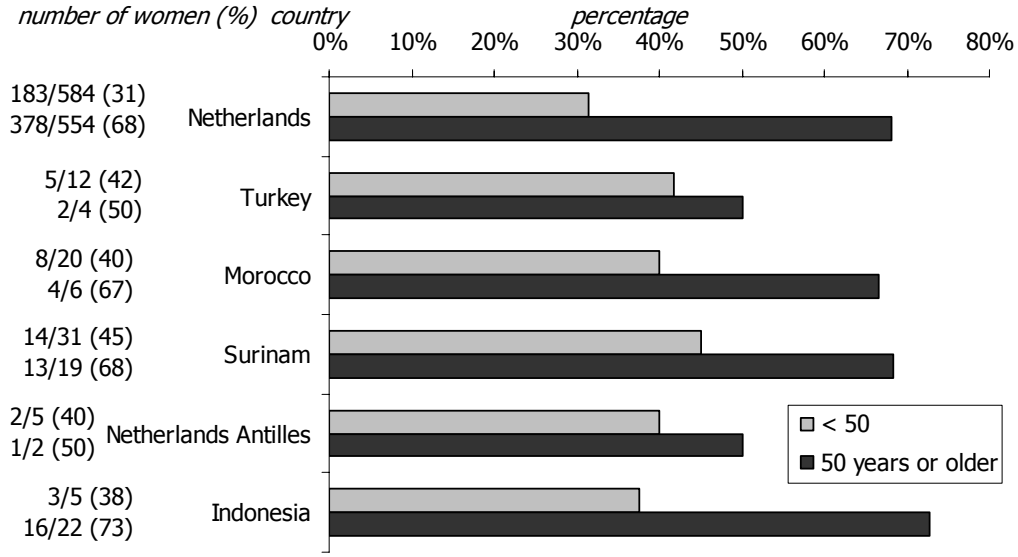
The age standardised incidence rate for cervical cancer in North-Holland was 8.2 per 100000 women in 1988-1998 (table 2) (9-11). For women born in Turkey (10.5), Morocco (15.3) and Surinam (12.9), the incidence was clearly higher. For women who were born in Indonesia and the Netherlands Antilles/Aruba, the incidence was some what below the rate for the total of North-Holland. With the exception of Turkish women, the incidence rate among migrant women in the North-Holland was below the rate in their country of origin.

Table 3. Observed (O) and expected (E) numbers of cervical cancer in North-Holland according to country of birth for the period 1988-1998 (reference population: Netherlands 1989-1997) (1)

country of birth	*area of residence*								
	Amsterdam			*other North-Holland*			*total North-Holland*		
	O	*E*	*O/E-ratio (95% CI)*	*O*	*E*	*O/E-ratio (95% CI)*	*O*	*E*	*O/E-ratio (95% CI)*
Turkey	10	7.4	1.4 (0.6-2.5)	6	5.9	1.0 (0.4-2.2)	16	13.3	1.2 (0.7-2.0)
Morocco	22	9.4	2.3* (1.5-3.5)	4	2.9	1.4 (0.4-3.5)	26	12.3	2.1* (1.4-3.1)
Surinam	44	25.2	1.7* (1.3-2.3)	6	7.1	0.8 (0.3-1.8)	50	32.3	1.5* (1.1-2.0)
Netherlands Antilles/Aruba	4	3.7	1.1 (0.3-2.8)	3	3.0	1.0 (0.2-2.9)	7	6.7	1.0 (0.4-2.2)
Indonesia	7	10.2	0.7 (0.3-1.4)	23	18.8	1.2 (0.8-1.8)	30	29.0	1.0 (0.7-1.5)
other (including the Netherlands and unknown)	485	333.7	1.5* (1.3-1.6)	916	885.7	1.0 (1.0-1.1)	1401	1219.4	1.1* (1.1-1.2)
total	572	389.6	1.5* (1.4-1.6)	958	923.4	1.0 (1.0-1.1)	1530	1313.0	1.2* (1.1-1.2)

* $p < 0.05$ for the difference between the observed and expected number

The observed number of cervical cancers in North-Holland (table 3) was slightly increased in comparison to the national average (O/E-ratio 1.2; 95% CI 1.1-1.2). This was caused by the high incidence in Amsterdam (O/E-ratio 1.5; 95% CI 1.4-1.6). Among women in Amsterdam who were born in Morocco or Surinam, the number of cervical cancers was strongly increased. However, the number of cervical cancers among women in Amsterdam who were born in the remaining countries (mainly the Netherlands) was also strongly increased. Among women born in Turkey, the Netherlands Antilles/Aruba and Indonesia the observed incidence differed little from the national average.



Number (%) of women in North-Holland with cervical cancer with extension outside the uterus (TNM-stage II-IV) according to country of birth, 1988-1998

The figure shows for two age groups the percentage of patients with extension of the cancer outside the uterus (TNM-stages II-IV). There was no statistically significant difference in stage at diagnosis between the different age groups, although the percentage of advanced stages below the age of 50 was lower among women who were born in the Netherlands than among foreign-born women.

DISCUSSION

In the period 1988-1998 the incidence of cervical cancer in North-Holland was slightly increased in comparison to the national incidence (O/E-ratio 1.2). The incidence was strongly increased among women with residence in Amsterdam (O/E-ratio 1.5) and among women born in Morocco (O/E-ratio 2.1) and Surinam (O/E-ratio 1.5). There was no statistically significant difference in stage at diagnosis between Dutch women and migrant women.
Based on the increased relative risks, the lifetime risk for cervical cancer for women born in Morocco and Surinam can be estimated at 1.5% and 1.1%, respectively. The

average lifetime risk for the Netherlands is 0.7% (1 out of every 140 women will get the disease) (12). So, the increase in the absolute risk to get the disease is limited.
For the determination of a person as a migrant or not, only the country of birth was available in this study. Although this information is objective, it has the limitation that it is impossible to investigate for example second generation migrants or the different ethnic groups of Surinam. For 10% of the cases, the country of birth could not be retrieved, because in a number of hospitals this information is not available in the medical records. Because we included the 'unknown' cases into the rates for Dutch women, the incidence for migrant women was underestimated, while the incidence for Dutch women was overestimated.
Cancer incidence rates have been published for the Turkish province of Izmir (10) and for the Netherlands Antilles; data for the other foreign countries in this study are sparse. Therefore, we compared the observed rates in North-Holland with estimations from the International Agency for Research on Cancer (IARC) (9). The differences in incidence between migrants in North-Holland and their country of origin could have been caused by changes in life style of the migrants or the absence of cervical cancer screening in the countries of origin. Moreover, it is not impossible that the estimations are incorrect, for example because of incompleteness of the mortality registration, which has been used by the IARC for their estimations. Possibly, the cancer registry of Izmir is also incomplete. Finally it is unclear whether migrants with residence in the Netherlands are representative for the residents in their country of origin or only for selective groups.
In many studies, it has been shown that the human papilloma virus (HPV) is the main factor in the etiology of cervical cancer (13-16), and that this relation is independent from other risk factors and consistent in different countries (13). It can be concluded that over 90% of the cervical tumours is related to HPV-infection (13-15), and HPV-DNA is present in virtually all patients (16). There are no statistically significant differences in the prevalence of HPV between different countries (13). However, differences in the prevalence of the different HPV-subtypes have been demonstrated (13, 17). This could be an explanation for the differences in cervical cancer incidence in different populations.
In this study, apart from age group, no correction has been made for other factors that may have influenced the incidence, such as smoking, the number of sexual partners or socio-economic status. Differences in socio-economic status may explain part of the differences in health status between migrants and the Dutch population (18). However, information on these factors was not available in the cancer registry. Consequently, it was impossible to explain, for example, the high incidence among Dutch women in Amsterdam.
Mortality due to cervical cancer in the Netherlands has been decreasing for 40 years (a 60% decrease between 1960 and 2000). Probably, half of the decrease was the result of screening programmes (19). The existing programme is aimed at women between 30 and 60 years of age. Attendance in Amsterdam (46% in 1996) is the lowest of the province of North-Holland and is far below the target (60%) (personal communication E. Kenter, 1999). Although the attendance reached 53% in 1999, in particular the attendance of women born in Morocco and the Netherlands Antilles was still far below the target (table 4). Also in Gooi & Vechtstreek (4) and Flevoland (B.Schouten, per-

sonal communication, 1997) the attendance of migrant women was lower than of Dutch women.

Table 4. Percentage attendance (A) and protection grade (P) in the screening programme for cervical cancer in Amsterdam in 1996 and 1999

Country of birth	1996		1999	
	A	P	A	P
Netherlands	48	62	56	73
Turkey	49	54	53	60
Morocco	38	44	45	51
Surinam	46	55	52	62
Netherlands Antilles/Aruba	45	51	45	56
other	38	47	45	57
total	46	59	53	68

Source: Municipal Health Service, Amsterdam

The epidemiology of cancer among ethnic minorities may offer understanding of the aetiology and in biological factors which may differ for different ethnic groups (20). Besides, epidemiological research may contribute to the identification of population subgroups who are less accessible for preventive activities, treatment and follow-up, as has been demonstrated in the United States (21). In order to reduce differences in health status it is important to reach groups of people with health problems and to give them access to health care and prevention activities. The aforementioned outweighs arguments of institutions to decide not to register ethnicity. Systematic registration of ethnicity under the observation of privacy regulations is essential for epidemiological research if we want to diminish differences in health status, in accordance with (inter)national agreements and policy objectives (22).

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2.2 Breast cancer risk among first-generation migrants in the Netherlands

Visser O, Van der Kooy K, Van Peppen AM, Ory FG, Van Leeuwen FE. Breast cancer risk among first-generation migrants in the Netherlands.
Br J Cancer. 2004 Jun 1;90(11):2135-7.

ABSTRACT

Background
In view of the world-wide variation in breast cancer incidence this study aims to investigate breast cancer incidence in migrants in the Netherlands.
Methods
The number of cases of breast cancer in North-Holland and The Hague for the period 1988-1998 was determined on the basis of data available from the regional cancer registries of the Comprehensive Cancer Centres Amsterdam and West. Based on data from the Netherlands Cancer Registry, a comparison was made between the observed and the expected number of cases by country of birth.
Results
In 1988-1998, the standardised incidence ratio (SIR) for breast cancer in Northwest-Netherlands was statistically significantly reduced for women born in Surinam (0.56), Turkey (0.29) and Morocco (0.22). For women from the latter two countries, the SIR was considerably higher below the age of 50 (Turkey 0.35; Morocco 0.33) in comparison to older women (Turkey 0.22; Morocco 0.10). In women born in Indonesia, the opposite was found (<50 years 0.83; 50 years or older 1.03).
The proportion of women with advanced stages (III and IV) did not differ significantly between migrants and women born in the Netherlands.
Conclusion
Although the risk of breast cancer among women resident in the Netherlands but born in Surinam, Turkey and Morocco is still close to the risk in their country of origin, the higher risk in younger women compared to older women from Turkey and Morocco indicates that a change in the breast cancer risk profile towards the risk profile of native women is already occurring in first generation migrants.

INTRODUCTION

Breast cancer is the most common cancer in women world-wide. Its incidence is particularly low in Central- and East-Africa, as well as in East-Asia (Ferlay et al., 1998). Most western countries have high incidence rates, while the rates in the Netherlands are among the highest in the world (Van der Sanden et al., 1995). In the United States, differences in breast cancer incidence have been observed between different ethnic groups (Ziegler et al. 1993; Brinton et al., 1997). Studies of Japanese migrants to Hawaii have shown that breast cancer incidence adjusts to the incidence in the new homeland within one or two generations. This indicates that life style and environmental factors are important factors with regard to breast cancer risk (McPherson et al., 2000).
In the last decades, immigration has changed the composition of the population of the Netherlands, especially in the large cities. In 2002, 10 percent of the population of the Netherlands and even 28 percent of the population of Amsterdam was foreign-born (StatLine, 2003). Migrants originate primarily from the former Dutch colonies (Indonesia [former name: Dutch East-Indies], Surinam and the Netherlands Antilles), Turkey and Morocco.
In view of the large world-wide variation this study aims to investigate differences in the incidence of breast cancer between migrants and women born in the Netherlands.

MATERIALS AND METHODS

Cancer registry data

Data have been used from the cancer registries of the Comprehensive Cancer Centre Amsterdam (CCCA) and the Comprehensive Cancer Centre West (CCCW). Both are part of the nation-wide Netherlands Cancer Registry (Van der Sanden et al., 1995). Information is extracted by registration clerks from medical records in all regional hospitals. If available in the hospital, the country of birth is routinely collected. Because the country of birth is unknown in many hospitals, only cases with residence in The Hague and the province of North-Holland have been included in this study. For women who participated in the breast cancer screening and who had agreed to record linkage of screening data to the cancer registry, the country of birth in the cancer registry has been validated with the country of birth as available in the screening data. In case of discrepancy or missing data in the cancer registry, the country of birth as available in the screening data has been used.

Population data according to country of birth.

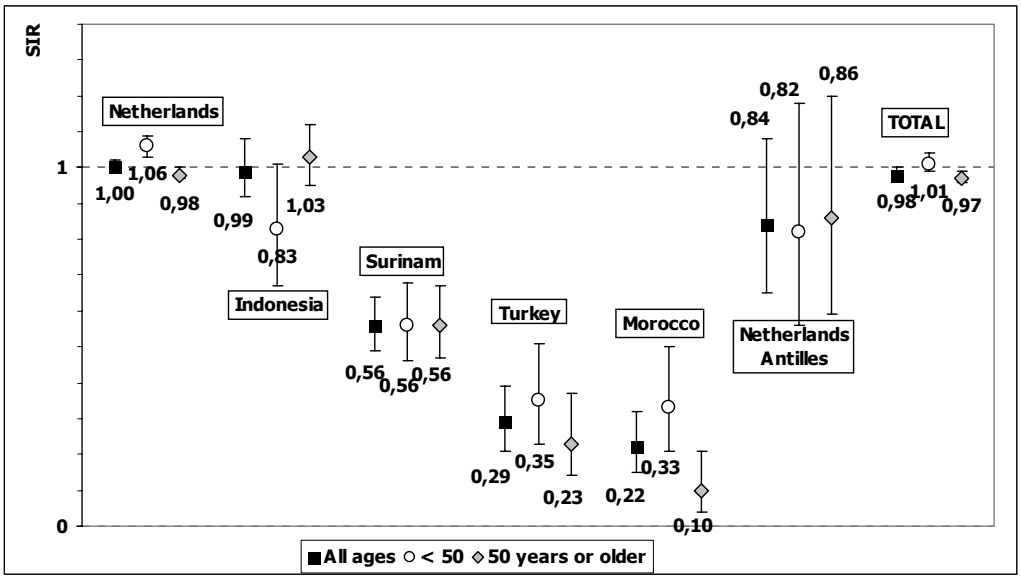
Statistics Netherlands receives population data from municipal population registers via the computerised population network that operates since October 1994. Annual overviews (as of 1995) of the population according to age group, sex and country of birth (Turkey, Morocco, Surinam, the Netherlands Antilles and Indonesia) for North-Holland and the city of The Hague have been used. For 1988-1994, estimations of Statistics Netherlands for 1992 and 1989-1994 (Surinam and the Netherlands Antilles only) have been used, completed with extrapolations for the remaining years. North-Holland and

The Hague combined cover 18 percent of the total population of the Netherlands, but approximately one third of the migrant population of the Netherlands.

Statistical methods

Based on the population data according to 5-year age category and country of birth and the age category specific breast cancer incidence rates from the Netherlands Cancer Registry for 1989-1998, expected numbers of breast cancer (E) for North-Holland and The Hague were calculated for women born in Turkey, Morocco, Surinam, the Netherlands Antilles and Indonesia, as well as for the total female population. The observed numbers (O) of breast cancer were adjusted for cases with unknown country of birth, assuming that the distribution according to country of birth for unknown cases was equal to the distribution of cases with known country of birth. The expected numbers were compared with the adjusted observed numbers and standardised incidence ratios (SIRs) were calculated as the ratio between the adjusted observed and expected numbers. Exact 95 percent confidence intervals (CI) based on the Poisson distribution of the adjusted O were calculated using STATA 7.0 (StataCorp. Stata Statistical Software: Release 7.0. College Station, TX: Stata Corporation).

RESULTS



Standardised incidence ratio (SIR) for invasive breast cancer according to country of birth in 1988-1998 in North-Holland & The Hague, the Netherlands (bars represent 95 percent confidence intervals; reference population: the Netherlands 1989-1998)

Breast cancer incidence

In 1988-1998, a total number of 16 499 invasive breast cancers were diagnosed in North-Holland (among which 28 percent in women with residence in Amsterdam) and 3 517 in The Hague (table). Eighty three percent of the women were born in the Neth-

erlands, while the percentage of foreign-born was 12 percent in The Hague and 13 percent in Amsterdam, compared to 6 percent in North-Holland (excluding Amsterdam). The country of birth was unknown for 8 percent of the cases.
The figure shows that the overall SIR for breast cancer in North-Holland & The Hague was almost equal to the national average (SIR 0.98; 95 percent confidence interval [CI]: 0.97, 1.00), slightly higher in women below the age of 50 (SIR 1.01) than in women of 50 years or older (SIR 0.97). For women born in Indonesia the SIR was also almost equal to the national average (SIR for all ages: 0.99, 95 percent CI: 0.92, 1.08), but for women below the age of 50 the rate was below the average (SIR 0.83, 95 percent CI: 0.67, 1.01). For women born in the Netherlands Antilles, we observed a SIR of 0.84 (95 percent CI: 0.65, 1.08) and for women born in Surinam a statistically significantly decreased rate of 0.56 (95 percent CI: 0.49, 0.64) was found. Very low rates were observed for women born in Turkey (SIR 0.29, 95 percent CI: 0.21, 0.39) and Morocco (SIR 0.22, 95 percent CI: 0.15, 0.32). In women born in Turkey or Morocco, the SIRs were lower among women of 50 years or older than among women below the age of 50 (0.23 versus 0.35 and 0.10 versus 0.33, respectively).

Number of invasive breast cancers in Northwest-Netherlands (The Hague and North-Holland) according to TNM-stage and country of birth, 1988-1998

Country of birth	*All stages*		*TNM-stage at diagnosis (n=16 297)**	
	Number	*%†*	*Stages I-II (%¶)*	*Stages III-IV (%¶)*
Netherlands	16 702	83.3%	85%	15%
Western countries	1 233	6.2%		
- Indonesia	583	2.9%	85%	15%
- Germany	245	1.2%	83%	17%
- Other western countries	405	2.0%	82%	18%
Non-western countries	466	2.3%		
- Surinam	218	1.1%	83%	17%
- Turkey	40	0.2%	87%	13%
- Morocco	26	0.1%	86%	14%
- Netherlands Antilles	59	0.3%	78%	22%
- Other non-western countries	123	0.6%	82%	18%
Unknown	1 615	8.1%	84%	16%
Total	20 016	100.0%	85%	15%

* unknown TNM-stage was included in I-II; cases for which TNM was not applicable (n=202) and cases with residence in The Hague (n=3 517) excluded
† percentage calculated vertically
¶ percentage calculated horizontally

Stage distribution

The table shows the distribution according to TNM-stage and country of birth for women with invasive breast cancers in the province of North-Holland. Cases with unknown stage (two percent of all cases), mainly due to unknown tumour size, were considered as localised. Eighty five percent of all cancers were localised (stage I or II). Fifteen percents of the patients had locally advanced disease or distant metastases (stages III or IV). The proportion of advanced stages ranged from 13% for women born in Turkey to 22% for women born in the Netherlands Antilles. A logistic regres-

sion analysis showed that, corrected for age group, the proportion of patients with advanced disease did not differ significantly between foreign-born women and women born in the Netherlands (15%).

DISCUSSION

The risk of breast cancer among women resident in the Netherlands but born in Surinam, Turkey and Morocco is still close to the risk in their country of origin. Although no national incidence data are available for these countries, estimates for the year 1990 show incidence rates that were 48 percent, 29 percent and 35 percent, respectively, of the rate for the Netherlands (Parkin et al, 1999). In the Netherlands Antilles, the incidence was 60.9 per 100 000 women (European standardised rate) in 1987-1991, about 60 percent of the rate of the Netherlands during that period (Schakenraad et al., 1995). The relatively high breast cancer risk of women born in the Netherlands Antilles with residence in the Netherlands, is probably due to selective migration of higher educated women to the Netherlands. Until recently, further education was one of the main motives for women to migrate to the Netherlands.

Although the screening attendance was low for women born in non-western countries (personal communication A.M. van Peppen), the percentage of cases with advanced stages was not significantly different from the percentage in women born in the Netherlands. In part, this may be explained by the relatively low number of cases among women born in non-western countries in the age group eligible for screening. Of all cases in women born in Turkey, 61 percent occurred in women below 50. For women born in Morocco this percentage was even 77, compared to 25 percent for women born in the Netherlands.

The low incidence of breast cancer in women born in Turkey and Morocco can probably be attributed to differences in risk factors for breast cancer in comparison to native women, especially in relation to reproduction. Compared to women of Dutch descent, women born in Turkey and Morocco have more children and have their first child at an earlier age. Due to the fact that these women came to the Netherlands as a partner of (male) migrant workers, the percentage of unmarried women without children is negligible (StatLine, 2003). Reproductive factors in women born in Surinam are intermediate between those in native women and women born in Turkey or Morocco. So, it is not surprising that breast cancer incidence among women born in Surinam is also in between the rates for women of Dutch descent and women born in Turkey or Morocco. The smallest differences as far as reproductive factors are concerned exist between women of Dutch descent and women born in the Netherlands Antilles. This probably explains why breast cancer risk among these women is close to the risk for women of Dutch descent.

The higher breast cancer risk in younger women (below the age of 50) born in Morocco or Turkey when compared to older women, is probably caused by a change in risk factors in younger women, such as lower parity. The slightly lower breast cancer risk for women below the age of 50 born in Indonesia (SIR 0.83) is remarkable, although the decrease is not statistically significant. Possibly this reflects differences between older and younger women born in Indonesia. Older women are mainly of Caucasian (Dutch) origin with a risk factor profile resembling that of Dutch women,

while younger women born in Indonesia, especially those born after the independence of Indonesia in 1949, are more often of ethnic Indonesian origin. So, the risk factor profile of young women born in Indonesia is more likely to differ from the risk factor profile of Dutch women than that of older women born in Indonesia.
In conclusion, in Northwest-Netherlands, women born in Surinam, Turkey and Morocco have a significantly decreased breast cancer risk when compared to women born in the Netherlands. It will be of interest to examine the risk of second generation migrants in the future.

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2.3 Results of breast cancer screening in first generation migrants in Northwest-Netherlands

Visser O, Van Peppen AM, Ory FG, Van Leeuwen FE. Results of breast cancer screening in first generation migrants in Northwest-Netherlands.
Eur J Cancer Prev. 2005 Jun;14(3):251-255.

ABSTRACT

Background
To determine breast cancer screening results according to country of birth data were used from the breast cancer screening organisation of the Comprehensive Cancer Centre Amsterdam, the Netherlands.
Results
Overall (age adjusted) attendance of the breast cancer screening was 76 percent for women aged 50-69. Attendance was significantly lower for women born in non-western-countries (Surinam 59%, Turkey 44%, Morocco 37%) and for women with residence in Amsterdam (68%). Referral and detection rates for women from non-western countries were 5.1 and 2.2 per 1000 screened women, respectively, compared to 8.8 and 4.0 for women born in the Netherlands ($p<0.05$). The positive predictive value was 45 percent for women born in the Netherlands and western countries and 43 percent for women born in non-western countries.
Conclusions
Although women born in non-western countries attend breast cancer screening less frequently than women born in the Netherlands, they also have a low detection rate. The latter finding justifies a passive attitude towards the low attendance.

INTRODUCTION

Breast cancer is the most common cancer in women world-wide. Incidence rates by country, however, show large variations. Breast cancer incidence is particularly low in Central- and East-Africa, as well as in East-Asia (Ferlay et al., 1998). Most western countries have high breast cancer incidence rates, while the rates in the Netherlands are among the highest in the world (Van der Sanden et al., 1995). In the United States, differences in breast cancer incidence have been observed between different ethnic groups (Ziegler et al. 1993; Brinton et al., 1997). Studies of Japanese migrants to Hawaii have shown that breast cancer incidence adjusts to the incidence in the new homeland within one or two generations. This indicates that life style and environmental factors are important factors with regard to breast cancer risk (McPherson et al., 2000).
In the last decades, extensive immigration has changed the composition of the population of the Netherlands, especially in the large cities. On January 1st 2003, 19 percent of the population of the Netherlands (ten percent first generation, nine percent second generation) and even 47 percent of the population of Amsterdam (28 percent first generation, 19 percent second generation) was of foreign origin (StatLine, Statistics Netherlands). Migrants originate primarily from the former Dutch colonies (Indonesia [former name: Dutch East-Indies], Surinam and the Netherlands Antilles) as well as Turkey and Morocco. There is also a large population of German origin. The vast majority of the second generation is still below the age of 30.
In 1990, a national breast cancer screening programme for women between 50 and 70 years was started in the Netherlands, its primary goal being a reduction in mortality due to breast cancer. In 1999, the programme was extended to women between 70 and 75 years old. As a result of the screening, breast cancer incidence in the Netherlands increased by over 20 percent between 1990 and 1998 and breast cancer was diagnosed at an earlier stage (Van Dijck et al., 2000). Moreover, since 1997 a decrease in mortality was observed in the age groups 55-65 and 65-75, which is probably also related to the breast cancer screening (Verbeek and Broeders, 2003).
In view of the large world-wide variation of breast cancer incidence this study aims to investigate whether the results of the breast screening were equal for women of Dutch descent and migrant women.

MATERIALS AND METHODS

Data on breast cancer screening

The Comprehensive Cancer Centre Amsterdam (CCCA) hosts one of the nine regional organisations, responsible for breast cancer screening in the region of the CCCA, which covers the province of North-Holland and the major part of the province of Flevoland. The total population numbered 2.8 million on January 1st, 2003. Breast cancer screening for women aged 50-69 years started in 1990 and was extended in the region gradually, to reach region-wide coverage in 1997. As of 1999, women aged 70-74 years are also invited. Women are invited every other year for mammography in mobile screening units. Population data are derived from municipal population registers via the computerised population network, which operates since October 1994. These

data include the country of birth and as of 1995, the country of birth is available for almost all women.
For this study, screening data have been used of women aged 50-74 years who were invited and/or screened in a second or subsequent round between January 1st 1995 and December 31st 2002. Age has been calculated as the age at January 1st. For the most common countries of birth (Netherlands, Indonesia, Germany, Surinam, Turkey, Morocco and the Netherlands Antilles), the attendance rate (percentage of women screened after invitation and one recall invitation), the referral rate (RR; number of referred women per 1000 screened women), the detection rate (DR; number of referred women diagnosed with breast cancer per 1000 screened women), the positive predictive value (PPV; number of breast cancers in referred women) and the interval carcinoma rate (IR; number of non-referred women diagnosed with breast cancer within 24 months after screening per 1000 screened women) have been calculated. Ductal carcinoma *in situ* was included in the number of breast cancers. Age-standardised rates for women aged 50-69 years have been calculated by taking the average of the rates for 50-54 years, 55-59 years, 60-64 years and 65-69 years. The countries of birth have been divided into western countries (all European countries, Australia, Canada, Japan, New Zealand, the United States of America and Indonesia) and non-western countries (all other countries). In this study, Indonesia is regarded as a western country, because Dutch residents born in Indonesia are predominantly of Dutch descent. They mainly returned to the Netherlands in the 1940s. After the independence in 1949, immigrants from Indonesia were more often ethnic Indonesian, but their numbers are relatively small.

Table 1. Attendance of women aged 50-69 years in the breast cancer screening programme of the Comprehensive Cancer Centre Amsterdam in second or subsequent rounds according to country of birth, 1995-2002

Country of birth	*Area of residence*					
	Amsterdam		*Outside Amsterdam*		*Total*	
	invited women	*attendance rate**	*invited women*	*attendance rate**	*invited women*	*attendance rate**
Netherlands	152 440	72%	571 050	81%	724 490	79%
Western countries:						
- Indonesia	7 440	66%	16 276	73%	23 716	71%
- Germany	2 375	63%	6 683	72%	9 058	69%
- Other western countries	7 446	54%	11 498	62%	18 944	59%
Non-western countries:						
- Surinam	13 728	57%	6 042	61%	19 770	59%
- Turkey	4 310	43%	4 256	45%	8 566	44%
- Morocco	6 086	36%	1 931	38%	8 017	37%
- Netherlands Antilles	1 746	57%	2 302	60%	4 048	59%
- Other non-western countries	4 470	49%	4 444	54%	8 914	51%
Total**	200 053	68%	624 863	79%	824 916	76%

* age-adjusted
** including women with unknown country of birth and women born at international territory

Statistical methods

Crude referral, detection and interval carcinoma rates, as well as the positive predictive values for women born outside the Netherlands were compared to the rates for women born in the Netherlands using the Chi^2 test.

RESULTS

Screening attendance

In the region of the CCCA, the number of invited women aged 50-69 years in second or subsequent rounds increased from 119 860 in 1995/96 to 266 820 in 2001/2002. In 1995-2002 a total of 824 916 women were invited. The age adjusted attendance rate was 76 percent for all women combined (table 1). In Amsterdam, the attendance rate was only 68 percent, compared to 79 percent in the remaining area. Women born in the Netherlands had the highest attendance rate (79 percent), while for all foreign-born women attendance was below the average. For women born in Germany or Indonesia, the attendance rate was around 70 percent. For women born in other western countries or in non-western countries, the attendance rate was 60 percent or lower. Very low attendance rates were observed for women born in Turkey and Morocco (44 percent and 37 percent, respectively). For all countries of birth, attendance in Amsterdam was lower than outside Amsterdam, but the largest difference (nine percent) was observed for women born in the Netherlands and Germany. For women born in non-western countries the difference was much smaller.
Table 2 shows that the attendance for all women combined was almost equal for the four age groups below 70 (50-54, 55-59, 60-64 and 65-69). Attendance in women of 70 years or older was about 10 percent lower. Women born in Turkey and Morocco attended clearly more often below the age of 60, when compared to women of 60 years or older.

Table 2. Attendance in the breast cancer screening programme of the Comprehensive Cancer Centre Amsterdam in second or subsequent rounds according to age group and country of birth, 1995-2002

Country of birth	*Age group*				
	50-54	*55-59*	*60-64*	*65-69*	*70+**
Netherlands	78%	80%	80%	77%	68%
Western countries:					
- Indonesia	70%	70%	72%	71%	61%
- Germany	68%	70%	72%	67%	60%
- Other western countries	60%	60%	58%	57%	51%
Non-western countries:					
- Surinam	61%	61%	58%	55%	46%
- Turkey	50%	48%	40%	39%	33%
- Morocco	39%	39%	36%	33%	27%
- Netherlands Antilles	63%	62%	59%	50%	32%
- Other non-western countries	54%	52%	50%	49%	34%
Total**	76%	77%	77%	76%	67%

* 1999-2002
** including women with unknown country of birth and women born at international territory

Referral and detection rates

In 1995-2000 in second and subsequent screening rounds, 3 535 out of 408 963 screened women aged 50-69 years were referred to a hospital for further examination. The age adjusted referral rate was 8.7 per 1000 screened women (table 3). The referral rates for women born in the Netherlands and in western countries were almost equal (8.8 and 8.9, respectively). The referral rate for women born in Indonesia was slightly higher (9.9), while the rate for women born in Germany was slightly lower (6.9), but this difference with women born in the Netherlands was not statistically significant. The referral rate for women born in non-western countries was only 5.1, almost half the rate for all women combined ($p<0.05$ when compared to women born in the Netherlands). Only for women born in the Netherlands Antilles the referral rate was close to the average for all women combined.

Table 3. Referral, detection and interval carcinoma rates for women aged 50-69 years in the breast cancer screening programme of the Comprehensive Cancer Centre Amsterdam in second or subsequent rounds according to country of birth, 1995-2000

Country of birth	*screened women*	*RR**	*DR**	*PPV**	*IR**
Netherlands	373 432	8.8	4.0	45%	2.2
Western countries:	21 521	8.9	4.0	45%	2.4
- Indonesia	10 881	9.9	4.7	47%	1.9
- Germany	4 127	6.9	3.4	49%	3.1
- Other western countries	6 513	8.3	3.3	39%	2.2
Non-western countries:	13 896	5.1†	2.2†	43%	1.2†
- Surinam	6 690	4.5†	1.5†	38%	1.5
- Turkey	1 943	4.0†	1.8†	33%	2.1
- Morocco	1 493	4.6	0.8	17%	0.0
- Netherlands Antilles	1 378	8.5	6.8	75%	1.4
- Other non-western countries	2 392	6.9	2.8	32%	0.5
Total**	408 963	8.7	3.9	45%	2.2

† $p<0.05$ when compared to women born in the Netherlands

* RR = age-adjusted referral rate (number of referrals per 1000 screened women); DR = age-adjusted detection rate (number of breast cancers in referred women per 1000 screened women); PPV = age-adjusted positive predictive value (number of breast cancers per 100 referred women); IR = age-adjusted interval carcinoma rate (number of breast cancers in non-referred women within 2 years after screening per 1000 screened women)

** including women with unknown country of birth and women born at international territory

Breast cancer (DCIS included) was diagnosed in 1 577 out of 3 535 referred women (PPV 45 percent). The age adjusted detection rate for all women combined was 3.9 per 1000 screened women in 1995-2000 (table 3). The detection rates for women born in the Netherlands and western countries were close to this average and the PPV was almost equal. In women born in non-western countries the detection rate was only 2.2 ($p<0.05$ when compared to women born in the Netherlands). Very low detection rates were observed for women born in Surinam, Turkey and Morocco (1.5, 1.8 and 0.8, respectively). Due to very small numbers (only 2 cancers detected) the rate for women born in Morocco was not statistically significantly different from the rate for women born in the Netherlands. The detection rate for women born in the Netherlands Antilles was rather high (6.8 per 1000 screened women), but due to small numbers this was

not statistically significant either. The PPV of all non-western women combined (43 percent) was almost equal to the PPV for women born in the Netherlands (45 percent). Table 3 also shows the interval carcinoma rates (DCIS included). Like the referral and detection rates, the interval carcinoma rates for women born in non-western countries were about half the rates of women born in the Netherlands ($p<0.05$), with the exception of women born in Turkey (2.1).

DISCUSSION

Attendance rates for breast cancer screening for women born in non-western countries are lower than for women born in the Netherlands and western countries. Women born in Morocco and Turkey have the lowest attendance rate, followed by women born in Surinam. The referral and detection rates of attending women born in non-western countries are also low, but the positive predictive value is almost equal to the positive predictive value of women born in the Netherlands and western countries.

A low screening attendance of especially women born in Morocco and Turkey, in comparison to women of Dutch descent, has also been observed in cervical cancer screening in the Netherlands (Visser et al., 2003). However, in cervical cancer screening, the attendance rate of Dutch women is also relatively low and the difference between migrant women and women born in the Netherlands is smaller than for breast cancer screening. The relatively low attendance of migrant women in the breast cancer screening may be related to the higher average age of women invited to the breast cancer screening (50-69) when compared to the cervical cancer screening (30-60). For women born in Turkey and Morocco, we found a clear association between age and attendance (the higher the age, the lower the attendance).

This study did not investigate the motives of women for non-attendance. However, a pilot study among Turkish women about (non-)attendance of the cervical cancer screening, revealed that command of the Dutch language and contentment with the general practitioner were associated with attendance, while 'absence of symptoms' has often been mentioned as a reason for non-attendance (Lâle et al., 2003). Absence of symptoms could also be a motive for not attending the breast cancer screening. Because the invitational letter for breast cancer screening is in Dutch, command of the language can also be associated with the (non-)attendance of Turkish and Moroccan women in the breast cancer screening, as the ability of these women to speak and understand the Dutch language is often poor. The majority of women born in Surinam or the Netherlands Antilles, however, speak Dutch and this may be an explanation for their higher attendance when compared to women born in Turkey or Morocco. Finally, religion (most women born in Morocco and Turkey are Moslem) may also have influenced the attendance.

In other countries differences in attendance to screening programmes have also been observed for various ethnic minorities, for example in the United Kingdom, Singapore and the United States (Kernohan, 1996; Seow et al., 1997; Suarez et al., 1994). In Sweden, immigrants from non-Nordic countries were more than twice as likely to be non-attenders compared with Swedish-born women (Lagerlun et al., 2002).

Although attendance of foreign-born women in Amsterdam was slightly lower than outside Amsterdam, residence in Amsterdam was of less relevance than for women of

Dutch descent. In high-income districts of Amsterdam, breast cancer surveillance outside the screening programme, for example because of an increased breast cancer risk, may be an explanation for the relatively low attendance of women of Dutch descent in Amsterdam when compared to women residing outside Amsterdam. In low-income districts, there may be an association with socio-economic status.
The low referral, detection and interval carcinoma rates in women born in non-western countries reflect the low breast cancer incidence in these women (Visser et al, 2004). The low incidence of breast cancer in women born in Turkey and Morocco can probably be attributed to differences in risk factors for breast cancer in comparison to native women, especially in relation to reproduction. Compared to women of Dutch descent, women born in Turkey and Morocco have more children and have their first child at an earlier age. Due to the fact that these women came to the Netherlands as a partner of (male) migrant workers, the percentage of unmarried women without children is negligible (StatLine, Statistics Netherlands). Use of hormones during menopause is probably also lower than among women of Dutch descent. Reproductive factors in women born in Surinam are intermediate between those in native women and women born in Turkey or Morocco. So, it is not surprising that breast cancer incidence among women born in Surinam is also in between the rates for women of Dutch descent and women born in Turkey or Morocco. The smallest differences as far as reproductive factors are concerned exist between women of Dutch descent and women born in the Netherlands Antilles. This probably explains why breast cancer risk among these women is close to the risk for women of Dutch descent.
In conclusion, the majority of women born in Turkey and Morocco and more than one third of the women born in Surinam do not attend breast cancer screening. Because these women also have a low breast cancer risk, a passive attitude towards the low attendance of first generation migrants seems as yet justified. This may not apply to second generation migrants. It will, however, take at least 20 to 30 years before second generation migrants are old enough to participate in breast cancer screening or develop breast cancer in substantial numbers.

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3

THE ENVIRONMENT AND CANCER

3.1 Incidence of cancer in the area around Amsterdam Airport Schiphol in 1988-2003; a population-based ecological study

Visser O, Van Wijnen JH, Van Leeuwen FE. Incidence of cancer in the area around Amsterdam Airport Schiphol in 1988-2003; a population-based ecological study. BMC Public Health (accepted for publication)

ABSTRACT

Background
Amsterdam Airport Schiphol is a major source of complaints about aircraft noise, safety risks and concerns about long term adverse health effects, including cancer. We investigated whether residents of the area around Schiphol are at higher risk of developing cancer than the general Dutch population.
Methods
In a population-based study using the regional cancer registry, we estimated the cancer incidence during 1988-2003 in residents of the area surrounding Schiphol. We defined a study area based on aircraft noise contours and 4-digit postal code areas, since historical data on ambient air pollution were not available and recent emission data did not differ from the background urban air quality.
Results
In residents of the study area 13 207 cancer cases were diagnosed, which was close to the expected number, using national incidence rates as a reference (standardized incidence ratio [SIR] 1.02). We found a statistically significantly increased incidence of hematological malignancies (SIR 1.12, 95% confidence interval [CI]: 1.05, 1.19), mainly due to high rates for non-Hodgkin lymphoma (SIR 1.22, 95% CI: 1.12, 1.33) and acute lymphoblastic leukemia (SIR 1.34, 95% CI: 0.95, 1.83). The incidence of cancer of the respiratory system was statistically significantly decreased (SIR 0.94, 95% CI: 0.90, 0.99), due to the low rate in males (SIR 0.89). In the core zone of the study area, cancer incidence was slightly higher than in the remaining ring zone (rate ratio of the core zone compared to the ring zone 1.05, 95% CI 1.01, 1.10). This was caused by the higher incidence of cancer of the respiratory system, prostate and the female genital organs in the core zone in comparison to the ring zone.
Conclusions
The overall cancer incidence in the Schiphol area was similar to the national incidence. The moderately increased risk of hematological malignancies could not be explained by higher levels of ambient air pollution in the Schiphol area. This observation warrants further research, for example in a study with focus on substances in urban ambient air pollution, as similar findings were observed in Greater Amsterdam.

BACKGROUND

Amsterdam Airport Schiphol is one of the main airports of Europe. The airport is a major source of complaints about aircraft noise, noise related adverse health effects and – especially since the crash of an airplane in a suburb of Amsterdam on October 4th 1992 – about safety risks. A longstanding subject of concern of the surrounding population is the exposure to aviation fuels and their combustion products and an alleged increase of cancer risk. Particularly in warm summers the smell of aviation fuels can be distinguished outside the airport grounds. Aircraft emissions vary with the engine type, the engine load and the kind of fuel. Combustion of aviation fuels results in CO_2, CO, C_e, NO_x ,particles, and a great number of other organic compounds, among which a number of carcinogens [1]. Among the emitted polycyclic aromatic hydrocarbons no compound characteristic for aircraft engines has been detected so far.
A committee of the Health Council of The Netherlands recently reviewed the data on the health impact of large airports [2]. It was concluded that, generally, integrated health assessments are not available. In the last 30 years, several adverse health effects in relation to exposure to aircraft noise have been the subject of study, such as the use of tranquillizers, the prevalence of bronchitis and cardiovascular disease as well as child stress responses and cognition [3-6]. However, little information is available in the international literature on cancer risk in relation to airports.
In the late 1980s, mortality due to cancer in the community of Haarlemmermeer, which hosts Schiphol, was investigated by the Municipal Health Service of Amsterdam on request of the general practitioners in the area [7]. The total cancer mortality and the lung cancer mortality in Haarlemmermeer during 1981-86 did not differ statistically significantly from the cancer mortality in the two standard populations that were used. The mortality due to non-Hodgkin lymphoma (NHL) was statistically significantly increased, but conclusions as to the cause of the excess mortality were not possible.
In the 1990s, we carried out a first study on the incidence of cancer in the vicinity of Schiphol, as part of the health surveillance of the resident population of the Schiphol area [8]. During 1988-1993, the incidence of cancer in the area around Schiphol was close to the national average. The differences in incidence of certain types of cancer in comparison to the national average, as well as those between two study areas characterized by different levels of increased aircraft noise, were considered to be most likely due to differences in life style, such as smoking. In order to investigate whether cancer risk of the resident population of the Schiphol area (in comparison to the national average) changed since 1988-1993, we continued monitoring cancer incidence and we report here on the second, much larger population-based study of the cancer incidence around Schiphol.

METHODS

Definition of the study population and the study area

When we designed our first study, relevant exposure data on the ambient air quality around Schiphol airport were lacking and we could not define a study population exposed to increased ambient levels of aircraft emissions. The airport itself has no permanent residents and the most heavily exposed population – the airport personnel and

the travelers – cannot be defined geographically. Therefore, we defined our study population as the population most heavily exposed to increased levels of aircraft noise. Since 1994, the ambient air quality outside Schiphol has been monitored and no differences with the background urban air quality have been reported for the compounds that were measured [9]. Table 1 summarizes the results of the three monitoring locations in the Schiphol area.

Table 1. Summary of the results in µg/m³ (except benzo(a)pyrene: ng/m³) of the air quality monitoring system of the Schiphol area in 2002

Pollutant	*Unit*	*Limit*	*Location of monitoring station*		
			Badhoevedorp	*Oude Meer*	*Hoofddorp*
NO_2	year average	40[a]	38	38	31
	maximum	200[b]	163	544(1x>200)	124
CO	P98 (8 hours)	9 000	112	100	88
	P99.9	40 000	134	165	160
O_3	maximum	240[c]	185	174	266 (2x>240)
PM_{10}	average (year)	40[d,e]	26	24	28
	maximum (24 hours)	50[d,f]	81 (13x>50)	81 (8x>50)	132 (22x>50)
Benzene	year average	10	1.4	1.1	0.7
Black smoke	P98 (24 hours)	90[g]	42	48	34
Benzo(a)pyrene	year average	1	0.14		

[a] as of 1-1-2010; [b] exceeding of the limit no more than 18 times per annum; [c] exceeding of the limit not more than 48 hours; [d] including factor 1.3; [e] as of 1-1-2005; [f] exceeding of the limit no more than 35 times per annum; [g] the limit expired in July 2001
PM_{10} = particulate matter <10 µm

However, it is possible that exposure to aircraft emissions has been greater in the past when aircraft engines used to be technologically and ecologically less advanced. Also, we cannot exclude that certain carcinogenic compounds specific to aviation combustion have not been monitored. Since most cancers have a long induction period and the noise contours are thought to reflect best the historical exposure of the surrounding population to aircraft emissions, we continued to use the levels of aircraft noise to define our study area. The aircraft noise levels of 1991 were available as so-called Kosten-units (Ku) [10]. We used the 35 Ku contour and extended the area with about 2 km outside the 35 Ku contour (figure 1). This total area (surrounded by the solid black line in figure 1) was redefined as 4-digit postal code areas (postal code areas surrounded by grey lines in figure 1). The four airstrips of the airport are easily recognized by noise levels over 50 Ku. We also defined a core zone for the 4-digit postal code areas within the 45 Ku contour (the area bordered by the blue line in figure 1), although we do not have empirical data showing that this zone corresponds to a zone with increased levels of ambient air pollution. The remaining study area surrounding the core zone we designated as 'ring zone'. The location of the three air quality monitoring stations (Badhoevedorp, Hoofddorp, Oude Meer) is also indicated in figure 1. The total study area with a population of 177 000 on 31 December 2003 comprised (parts of) five municipalities (table 2). Table 2 also includes figures on per capita income as approximation for socio-economic status.

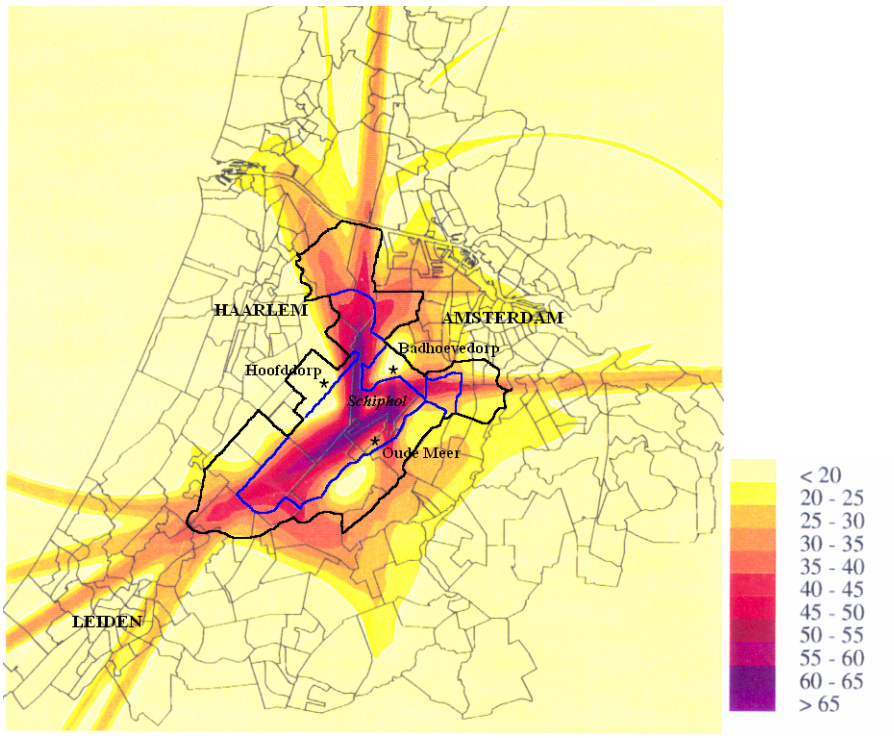

Figure 1. Noise exposure (in Kosten-units) in the Schiphol area in 1991. The area surrounded by the grey line indicates the core zone, the black line includes the total study area. The location of the three air quality monitoring stations are indicated by asterisks (*).

Population data

Annual population data covering the period 1995-2003 according to 4-digit postal code, 5-year age groups and sex, were available for all municipalities from Statistics Netherlands. For the period 1988-1994 we used data from the municipal administrations.

Cancer registry data

The Amsterdam Cancer Registry (ACR) is a regional, population-based cancer registry with complete regional coverage since 1988. The ACR is part of the nation-wide Netherlands Cancer Registry (NCR) [11]. Completeness of the NCR is estimated to be over 95%. The information is extracted from the medical records by registration clerks. Apart from demographic data, data are collected on tumor site, morphological classification (according to the International Classification of Diseases for Oncology [ICD-O], versions 1 and 2), stage of the tumor and treatment of the patients. The third version of the ICD-O was introduced in the NCR for cases diagnosed as of January 2001. Cases diagnosed in a hospital outside the ACR region but with residence in the ACR

region are routinely obtained from the national registry and included in our regional registry. Consequently, these cases could be included in the study.
We selected from the registry all cancer cases in the period 1988-2003 with residence in the area around Schiphol airport at the date of diagnosis. We stratified the cases according to type of cancer (or group of cancers), area of residence (core zone or the ring zone), 5-year age group and sex.

Table 2. Some characteristics of the Schiphol study area

Zone and municipality	*Postal codes*	*Inhabitants*		*Per capita* income (1998)*
		1-1-1988	*31-12-2003*	
Core zone		**30 590**	**31 850**	**€10 900**†
Haarlemmermeer	1161	8 300	7 820	€10 700
	1175, 1435-8, 2143	6 880	6 015	€11 000
	2132	7 815	10 965	€11 000
	2153	3 520	3 310	€10 500
Amstelveen	1182	4 075	3 740	€11 500
Ring zone		**131 210**	**144 870**	**€11 800**†
Haarlemmermeer	1171	10 750	11 770	€13 200
	2131	10 205	11 030	€11 400
	2151-2	11 925	22 260	€11 100
	2154-8, 2165	5 585	5 940	€10 300
Amstelveen	1181, 1183	31 145	30 385	€12 400
Amsterdam	1067, 1081-3	34 960	35 080	€14 500
Aalsmeer	1431-3	21 740	22 870	€11 300
Haarlemmerliede & Spaarnwoude	1165, 2064-5	4 900	5 535	€10 800
Total study area		**161 800**	**176 720**	**€11 700**†

* the national average in 1998 was €10 00
† weighed average, rounded to €100

Statistical methods

In our analysis, the incidence of cancer in the national population of the Netherlands served as the reference entity. The expected numbers of cancer (E) for the Schiphol area were calculated for three periods (1988-1993, 1994-1998 and 1999-2003), based on the population data of the Schiphol area (according to 5-year age category and sex) and the 5-year age category and sex-specific cancer incidence rates from the NCR. For the period 1988-1993 we used the average incidence rates of the NCR covering the period 1989-1993 [12], because data for 1988 were not available from the NCR. For the periods 1994-1998 and 1999-2003 we used NCR-data covering 1994-1998 and 1999-2003, respectively [13]. The expected numbers were compared with the observed numbers (O) and standardized incidence ratios (SIRs) were calculated as the ratio between the observed and expected numbers. Exact 95%-confidence intervals (CI) based on the Poisson distribution of O were calculated using STATA 7.0 (STATA Corporation. College Station, Texas, USA). Rate ratios (RR) for the core zone were calculated by dividing the standardized incidence ratio of the core zone by the rate of the ring zone. Ninety five percent CIs of RRs were calculated assuming a log-normal distribution [14].

Table 3. Observed (O) and expected (E) number of cancers in subjects with residence in the Schiphol area according to site, gender and period of diagnosis, 1988-2003

cancer site (ICD-10 code) and gender	*Total period (1988-2003)*				*1988-1993*			*1994-1998*			*1999-2003*		
	O	*E*	*SIR*	*95% CI*	*O*	*SIR*	*95% CI*	*O*	*SIR*	*95% CI*	*O*	*SIR*	*95% CI*
All malignancies (C00-C96)	13 207	13 007.9	**1.02**	1.00, 1.03	4 624	**1.02**	0.99, 1.05	4 220	**1.02**	0.99, 1.05	4 363	**1.00**	0.97, 1.03
adult males	6 697	6 713.7	**1.00**	0.97, 1.02	2 402	**1.02**	0.98, 1.06	2 145	**1.00**	0.96, 1.04	2 150	**0.98**	0.94, 1.02
adult females	6 436	6 235.3	**1.03** *	1.01, 1.06	2 190	**1.02**	0.97, 1.06	2 057	**1.05** *	1.01, 1.10	2 189	**1.03**	0.99, 1.07
children <15	74	58.9	**1.26**	0.99, 1.58	32	**1.54** *	1.06, 2.18	18	**0.98**	0.58, 1.55	24	**1.21**	0.77, 1.79
Head & neck (C00-C14)	282	272.9	**1.03**	0.92, 1.16	93	**0.99**	0.80, 1.22	91	**1.06**	0.85, 1.30	98	**1.05**	0.85, 1.28
males	162	176.9	**0.92**	0.78, 1.07	53	**0.84**	0.63, 1.10	56	**1.01**	0.76, 1.31	53	**0.91**	0.68, 1.19
females	120	96.0	**1.25** *	1.04, 1.49	40	**1.29**	0.92, 1.76	35	**1.16**	0.80, 1.61	45	**1.29**	0.94, 1.73
Gastrointestinal tract (C15-C26)	2 889	2 936.0	**0.98**	0.95, 1.02	1 034	**0.99**	0.93, 1.05	899	**0.98**	0.91, 1.04	956	**0.99**	0.93, 1.05
males	1 494	1 538.0	**0.97**	0.92, 1.02	517	**0.95**	0.87, 1.04	470	**0.97**	0.89, 1.07	507	**0.99**	0.90, 1.08
females	1 395	1 398.1	**1.00**	0.95, 1.05	517	**1.02**	0.93, 1.11	429	**0.98**	0.89, 1.08	449	**0.99**	0.90, 1.09
Respiratory system (C30-C34)	1 862	1 975.1	**0.94** *	0.90, 0.99	749	**1.00**	0.93, 1.07	542	**0.86** †	0.79, 0.94	571	**0.96**	0.88, 1.04
males	1 378	1 548.0	**0.89** †	0.84, 0.94	604	**0.96**	0.89, 1.01	386	**0.78** †	0.71, 0.87	388	**0.90**	0.82, 1.00
females	484	427.1	**1.13** *	1.03, 1.24	145	**1.15**	0.97, 1.35	156	**1.16**	0.98, 1.36	183	**1.10**	0.95, 1.27
Breast (C50)	2 087	1 983.6	**1.05**	0.99, 1.11	679	**1.00**	0.93, 1.08	678	**1.09** *	1.01, 1.18	730	**1.06**	0.99, 1.14
Female genital organs (C51-C58)	710	730.7	**0.97**	0.90, 1.05	252	**0.92**	0.81, 1.04	237	**1.02**	0.89, 1.16	221	**0.99**	0.87, 1.13
Prostate (C61)	1 291	1 230.9	**1.05**	0.99, 1.11	382	**1.05**	0.95, 1.16	470	**1.12** *	1.02, 1.22	439	**0.99**	0.90, 1.08
Bladder & other urinary tract (C65-C68)	543	517.2	**1.05**	0.96, 1.14	211	**1.15**	1.00, 1.31	172	**1.05**	0.90, 1.22	160	**0.94**	0.80, 1.10
males	425	390.0	**1.09**	0.99, 1.20	173	**1.24** †	1.06, 1.44	129	**1.04**	0.87, 1.24	123	**0.97**	0.81, 1.16
females	118	127.3	**0.93**	0.77, 1.11	38	**0.86**	0.54, 1.29	43	**1.07**	0.78, 1.44	37	**0.86**	0.61, 1.19
Hematological malignancies (C81-C96)	1 044	935.2	**1.12** †	1.05, 1.19	367	**1.12** *	1.01, 1.24	334	**1.15** *	1.03, 1.28	343	**1.09**	0.97, 1.21
males	598	507.6	**1.18** †	1.09, 1.28	210	**1.18** *	1.03, 1.36	184	**1.17**	1.00, 1.35	204	**1.18** *	1.03, 1.36
females	446	427.6	**1.04**	0.95, 1.14	157	**1.04**	0.88, 1.22	150	**1.12**	0.95, 1.32	139	**0.97**	0.82, 1.15
Hodgkin lymphoma	48	61.2	**0.78**	0.58, 1.04	19	**0.81**	0.48, 1.26	12	**0.68**	0.35, 1.18	17	**0.85**	0.50, 1.37
non-Hodgkin lymphoma	516	423.5	**1.22** †	1.12, 1.33	176	**1.17** *	1.01, 1.36	181	**1.36** †	1.17, 1.57	159	**1.14**	0.97, 1.33
plasma cell tumors	169	156.1	**1.08**	0.93, 1.26	59	**1.06**	0.81, 1.37	56	**1.09**	0.82, 1.42	54	**1.10**	0.82, 1.43
acute lymphoblastic leukemia	39	29.1	**1.34**	0.95, 1.83	17	**1.67**	0.97, 2.67	8	**0.91**	0.39, 1.79	14	**1.38**	0.75, 2.30
chronic lymphocytic leukemia	92	101.2	**0.91**	0.73, 1.11	33	**0.94**	0.65, 1.32	29	**0.82**	0.55, 1.18	30	**0.97**	0.65, 1.38
acute myeloid leukemia	109	97.8	**1.11**	0.92, 1.34	40	**1.18**	0.84, 1.61	33	**1.05**	0.72, 1.48	36	**1.11**	0.78, 1.54
other	71	66.2	**1.07**	0.84, 1.35	23	**1.15**	0.73, 1.72	15	**1.13**	0.63, 1.86	33	**1.00**	0.69, 1.41
Other sites	2 499	2 426.3	**1.03**	0.99, 1.07	857	**1.05**	0.98, 1.12	797	**1.05**	0.97, 1.12	845	**1.00**	0.93, 1.06
males	1 391	1 355.5	**1.03**	0.97, 1.08	485	**1.05**	0.96, 1.15	462	**1.08**	0.99, 1.18	444	**0.95**	0.87, 1.05
females	1 108	1 070.8	**1.03**	0.97, 1.10	372	**1.06**	0.95, 1.17	335	**1.00**	0.90, 1.11	401	**1.05**	0.95, 1.15

* p<0.05; † p<0.01; CI = confidence interval ; E = expected number ; O = observed number; SIR = standardized incidence ratio

RESULTS

In 1988-2003, a total of 13 207 cancers (6 739 in males, 6 468 in females) were diagnosed among residents of the Schiphol area (table 3), which included 2 352 cases among residents of the core zone. Table 3 shows, that the total number of observed cancers was close to the expected number (SIR 1.02, 95% CI: 1.00, 1.03), in males (SIR 1.00, 95% CI: 0.97, 1.02) as well as in females (SIR 1.03, 95% CI: 1.01, 1.06). The observed number of cancers of the respiratory system (predominantly lung cancer) in females was increased (SIR 1.13, 95% CI: 1.03, 1.24), but the number in both sexes combined was statistically significantly decreased (SIR 0.94, 95% CI: 0.90, 0.99). This was caused by a relatively low incidence in males (SIR 0.89, 95% CI: 0.84, 0.94). A similar pattern was observed for cancer of head and neck (SIR females 1.25, 95% CI 1.04, 1.49; SIR males 0.92, 95% CI 0.78-1.07).The incidence was statistically significantly increased for hematological malignancies (SIR 1.12, 95% CI: 1.05, 1.19, 1044 cases). The raised risk was most prominent in males (SIR males 1.18, 95% CI: 1.09, 1.28, SIR females 1.04, 95% CI: 0.95, 1.14). A statistically significantly increased incidence was observed for NHL (SIR 1.22, 95% CI: 1.12, 1.33, 516 cases), while the confidence interval for acute lymphoblastic leukemia (ALL; SIR 1.34, 95% CI: 0.95, 1.83, 39 cases) included unity. A relatively low rate was observed for Hodgkin lymphoma (SIR 0.78, 95% CI: 0.58, 1.04).Classification of lymphoid malignancies according to the WHO-classification, revealed relatively high rates for lymphoplasmocytic lymphoma (SIR 1.5, 95% CI: 1.1, 2.9), follicular lymphoma (SIR 1.5, 95% CI: 1.2, 1.8), diffuse large B-cell lymphoma (SIR 1.6, 95% CI: 1.4, 1.9) and T-cell lymphoma (SIR 1.4, 95% CI: 1.0, 1.8). The rates for plasma cell tumors (SIR 1.1, 95% CI 0.9, 1.3), small lymphocytic lymphoma/chronic lymphocytic leukemia (SIR 0.8, 95% CI: 0.6, 1.0) and other & unspecified lymphoma/leukemia (SIR 1.0, 95% CI: 0.8, 1.2) were not increased.
Cancer was diagnosed in 74 children up to 15 years of age, which was relatively high (SIR 1.26, 95% CI 0.99, 1.58), due to the higher than expected number of children with ALL (23 cases, SIR 1.59, 95% CI 1.01, 2.39).
For most cancer sites, the SIRs for the periods 1988-1993, 1994-1998 and 1999-2003 were quite similar. The increased risk of hematological malignancies was consistently observed in the three time periods. An increased number of breast cancer cases was observed in the 1994-1998 period (SIR 1.09, 95% CI 1.01, 1.18). An increased number of cancer of the bladder and other urinary organs in males was only observed in 1988-1993 (SIR 1.24, 95% CI 1.06, 1.44).

Cancer incidence in the core zone

Table 4 shows that cancer incidence in the core zone was slightly increased in comparison to the national incidence (SIR 1.06, 95% CI 1.02, 1.10) as well as in comparison to the ring zone (RR 1.05, 95% CI 1.01, 1.10), mostly because of an increased incidence in males (SIR 1.07, 95% CI 1.01, 1.13; RR 1.09, 95% CI 1.03, 1.16). Statistically significantly increased numbers in the core zone in comparison to the ring zone were observed for cancer of the respiratory system (RR 1.27, 95% CI 1.12, 1.45) and prostate (RR 1.17, 95% CI 1.02, 1.34) in males and for cancer of the genital organs in females (RR 1.24, 95% CI 1.04, 1.50), based on increased RRs for each specific site

Table 4. Number of cancer cases in subjects with residence in the Schiphol area according to site, gender and area of residence, 1988-2003

cancer site (ICD-10 code) and gender	*area of residence*									
	ring zone				*core zone*					
	number	*parameter*			*number of*	*parameter*				
	of cases	*SIR#*		*95% CI*	*cases*	*SIR#*		*95% CI*	*RR##*		*95% CI*
All malignancies (C00-C95)	10 855	1.01		0.99, 1.03	2 352	1.06	*	1.02, 1.10	1.05	*	1.01, 1.10
adult males	5 440	0.98		0.96, 1.01	1 257	1.07	*	1.01, 1.13	1.09	*	1.03, 1.16
adult females	5 356	1.03		1.00, 1.06	1 080	1.04		0.98, 1.11	1.01		0.95, 1.08
children (<15)	59	1.25		0.95, 1.61	15	1.29		0.72, 2.13	1.04		0.59, 1.83
Head & neck (C00-C14)	238	1.06		0.93, 1.21	44	0.90		0.65, 1.21	0.85		0.61, 1.17
males	133	0.92		0.77, 1.09	29	0.89		0.59, 1.27	0.96		0.64, 1.44
females	105	1.32	*	1.08, 1.59	15	0.93		0.52, 1.53	0.70		0.41, 1.21
Gastrointestinal tract (C15-C26)	2 422	0.99		0.95, 1.03	467	0.96		0.87, 1.05	0.97		0.88, 1.07
males	1 240	0.98		0.92, 1.03	254	0.95		0.83, 1.07	0.97		0.85, 1.11
females	1 182	1.00		0.95, 1.06	213	0.97		0.85, 1.11	0.97		0.84, 1.12
Respiratory system (C30-C34)	1 484	0.91	*	0.86, 0.96	378	1.10		0.99, 1.22	1.21	*	1.08, 1.35
males	1 085	0.85	*	0.80, 0.90	293	1.08		0.96, 1.21	1.27	*	1.12, 1.45
females	399	1.13	*	1.02, 1.24	85	1.17		0.93, 1.44	1.04		0.82, 1.31
Breast (C50)	1 731	1.05	*	1.01, 1.11	356	1.04		0.93, 1.15	0.99		0.88, 1.11
Female genital organs (C51-C58)	567	0.93		0.86, 1.01	143	1.16		0.98, 1.37	1.24	*	1.04, 1.50
Prostate (C61)	1 044	1.02		0.96, 1.08	247	1.19	*	1.05, 1.35	1.17	*	1.02, 1.34
Bladder & other urinary tract (C65-C68)	468	1.09		0.99, 1.19	102	1.18		0.96, 1.43	1.16		0.93, 1.43
males	341	1.05		0.95, 1.17	84	1.26	*	1.01, 1.56	1.20		0.94, 1.52
females	100	0.93		0.76, 1.13	18	0.92		0.54, 1.44	0.98		0.60, 1.63
Hematological malignancies (C81-C96)	855	1.10	*	1.03, 1.18	189	1.17	*	1.01, 1.35	1.06		0.91, 1.24
males	483	1.16	*	1.06, 1.27	115	1.26	*	1.04, 1.51	1.09		0.89, 1.33
females	372	1.04		0.94, 1.15	74	1.06		0.83, 1.33	1.02		0.79, 1.31
Other sites	2 073	1.03		0.99, 1.08	426	1.02		0.93, 1.12	0.99		0.89, 1.10
males	1 148	1.03		0.97, 1.09	243	1.01		0.89, 1.14	0.98		0.85, 1.12
females	925	1.03		0.97, 1.10	183	1.04		0.90, 1.20	1.01		0.86, 1.18

* $p<0.05$
# reference population: the Netherlands 1989-2003
ratio of the SIR of the core zone and the SIR of the ring zone
CI = confidence interval ; SIR = standardized incidence ratio; RR = rate ratio

(cervix 1.20, corpus 1.04, ovary 1.55, vulva & other 1.17). In comparison to the national incidence only cervical cancer and ovarian cancer were increased (SIR cervix 1.29, corpus 1.00, ovary 1.32, vulva & other 0.98). In the core zone, the incidence rate of bladder cancer in males (SIR 1.26, 95% CI 1.01, 1.56; RR 1.20, 95% CI 0.94, 1.52) was also relativity high. The incidence of hematological malignancies was higher in the core zone than in the to the ring zone, but the increase was not statistically significant (RR 1.06, 95% CI 0.91, 1.24).

DISCUSSION

The major finding of our study is that total cancer incidence in the area around Schiphol airport was almost equal to the national cancer incidence (SIR 1.02). Furthermore, the incidence of hematological malignancies was statistically significantly increased, while the incidence of cancer of the respiratory system was statistically significantly decreased. We observed an excess risk in children aged 0-14 (SIR 1.26). The cancer incidence in the core zone was slightly increased in comparison to the ring zone, due to an excess risk of cancer of the respiratory tract and prostate in males and cancer of the genital organs in females.

As the overall incidence of cancer of the respiratory tract was decreased (SIR 0.94), this observation does not support a positive association between the airport and the occurrence of cancer of the respiratory tract. The incidence pattern of respiratory system cancer in the Schiphol area, i.e. low rates in males and somewhat higher rates in the core zone and among females, is well within the normal regional variation in the Netherlands. Because smoking is the most important risk factor for lung cancer [15], and there is evidence of substantial regional variation in smoking habits in the Netherlands [16], smoking is likely to be responsible for the differences in respiratory system cancer (mainly lung cancer) between the Schiphol area and the Netherlands overall. Unfortunately, no data on smoking habits according to postal code in the Schiphol area are available. Lung cancer incidence in the 1990s in males was lowest in high income areas in the Netherlands. In females, low rates were found in rural areas, while high rates were observed in urban areas [17]. The slightly increased incidence of cancer of the respiratory system in females is in accordance with the moderately urbanized status of the Schiphol area. The data on per capita income (table 2) support the assumption that the low incidence of cancer of the respiratory system in males is related to the high per capita income of the Schiphol area. However, within the Schiphol area only a weak association was observed between the incidence of lung cancer and per capita income by postal code area (data not shown). This may be due to relatively small numbers by postal code area and the long induction period of lung cancer as the regional variation in lung cancer incidence can best be explained by the smoking habits 10 to 30 years ago.

In a number of studies in urban areas an increase of lung cancer incidence or mortality was observed [18,19], mostly attributed to differences in smoking habits. However, there is increasing evidence for a relation between lung cancer risk and ambient air pollution [20,21]. Although we cannot exclude the possibility that the incidence of cancer of the respiratory system in the absence of the airport would even have been

lower than the observed incidence, the pattern of the observed incidence does not render this very likely.
The statistically significantly increased rate for breast cancer in 1994-1998 (SIR 1.09 for the total study area) is also within the observed regional variation in the Netherlands. Part of this variation can be explained by local variation in the start of the national screening program for breast cancer. The relatively high incidence of breast cancer in 1994-1998 is probably related to the start of screening in the Schiphol area in that period.
We do not have an explanation for the relatively high incidence of cancer of the female genital organs in the core zone (RR in comparison to the ring zone 1.24). Possibly, this is only a chance finding, as despite the large variation in risk factors for the specific sites the incidence of all specific sites was increased, while the SIR in comparison to the general population was not statistically significantly increased. An association with pollution has not been described for cancer of the female genital organs. Moreover, in the total study area the incidence of these cancers was not increased (SIR 0.97).
The most striking observation in our study is the increased incidence of hematological malignancies, which was observed consistently over three periods, mostly in males but also in females. The increase was more pronounced in the core zone. The increased incidence was mostly due to increased numbers of cases of ALL and NHL (especially lymphoplasmocytic lymphoma, follicular lymphoma, diffuse large B-cell lymphoma and T-cell lymphoma, but not small lymphocytic lymphoma/chronic lymphocytic leukemia [SLL/CLL]), while the incidence of Hodgkin lymphoma was decreased. However, pathology could not be reviewed in this study and different classification systems of lymphoma have been used by pathologists during the study period.
The moderately increased cancer incidence in children (about one supplementary case per year) was mainly caused by the increased number of cases of ALL, as ALL occurs mainly in children.
Also from a national perspective, the number of cases of NHL was markedly increased. In the Netherlands in 1989-1998, the highest rate of NHL in males was found in Greater-Amsterdam, which includes the Schiphol area (source: the Netherlands Cancer Registry). In females in Greater-Amsterdam, the incidence of NHL was also relatively high. Chance is not a likely explanation for our finding of an increased incidence of NHL, since the increase was consistently observed over three time periods. The relatively high incidence of NHL in the Schiphol area is also consistent with an increased mortality due to NHL already reported in Haarlemmermeer in 1981-1986 [7]. In several studies, an increased risk of hematological malignancies was found for farmers, which is related to the use of pesticides, infectious micro-organisms or working with beef cattle [22-27]. However, although the Schiphol area includes a few areas with intensive agricultural activities, the increased risk for hematological malignancies was also found in areas with few agricultural activities.
Several studies have shown that the incidence of NHL is correlated with nitrate in municipal drinking water due to nitrogen fertilizers [28,29] and is increased in urban/industrialized areas [30,31]. Hatzissabas et al found that the incidence of large cell high malignancy lymphomas is highest in industrialized regions with pollution of water supplies by more toxic and immunosuppressive substances, while CLL is more frequent in areas with rather low-dose chronic influences such as from the use of fertilizers and

pesticides in farming [32]. The pattern of NHL in the Schiphol area -increase of follicular and diffuse large B-cell lymphoma, but not SLL/CLL- might indicate a relation with pollution which is also found in urban areas.
However, an association between the incidence of hematological malignancies and the environment in the Schiphol area is not supported by the available data on ambient air quality. Measurements in 1989 at the airport grounds of Schiphol showed increased levels of ambient air pollutants, including polycyclic aromatic hydrocarbons which are probably or possibly carcinogenic according to the International Agency for Research on Cancer, but not in the direct vicinity outside the airport ground [33]. Morphology and composition of soot emitted by aircraft at Schiphol showed great similarities with soot emitted by the road traffic. Only different profiles of hydrocarbons in the range of C6–C12 in emissions from aircraft engines, aviation fuels and road traffic were reported. Since 1994, three locations in the vicinity of Schiphol are part of the provincial monitoring network for ambient air quality measurement [34]. During 1994-2002, the concentrations of the air pollutants NO2, CO, O3, PM10 (particulate matter <10 µm), benzo(a)pyrene, benzene and black smoke at the three locations in the Schiphol area were stable and well comparable to urban background levels in Amsterdam [9]. A more detailed investigation at 59 additional locations in the Schiphol area in 2000/2001 revealed that the average contribution of air traffic emissions and of aviation fuel storage and transfer to the total concentration of volatile hydrocarbons in the area around Schiphol were only 3%, and up to 5-7% at individual locations [35]. Road traffic contributed 28%. For CO, NO2 and PM10, no relevant influence of emissions of Schiphol on ambient pollutant levels could be determined. Although we cannot exclude the possibility that residents of the Schiphol area have been exposed to air pollutants that were not measured or that higher levels of air pollutants have existed in the past, the results of the ambient air quality monitoring and the source appointment of air pollutants render it unlikely that aircraft emissions have contributed substantially to the total levels of pollutants in the ambient air of the Schiphol area. It therefore seems unlikely that the increased incidence of hematological malignancies is specifically related to ambient air pollution caused by aircraft emissions.
Our results should be interpreted considering the strengths and limitations of the study design. An advantage is the availability of high quality data from a population-based cancer registry over a period of sixteen years. However, the use of the national cancer incidence as a reference has its limitations. Preferably, the cancer incidence in a population which is comparable to the Schiphol region as far as urbanization, socio-economic status and smoking habits, should be used. Unfortunately, such a reference population is not available. Another limitation of the study is that only cancer cases that were residents of the Schiphol area at the date of diagnosis were included in the study. Part of the original residents will have left the area, while others only recently settled in the area. The effect of migration (non-differential misclassification) usually results in an underestimation of the risk at study.

CONCLUSIONS

The overall cancer incidence in the Schiphol area was similar to the national incidence in the Netherlands. An association was found between residence in the Schiphol area

and a moderately increased incidence of hematological malignancies, especially NHL and ALL. However, the increased risk of hematological malignancies could not be explained by higher levels of ambient air pollution in the Schiphol area, while similarly increased rates were observed in Greater Amsterdam. Further studies, for example a study with focus on substances in urban ambient air pollution, are necessary in order to elucidate the causes of the observed association.

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3.2 Residential traffic density and cancer incidence in Amsterdam, 1989-1997

Visser O, Van Wijnen JH, Van Leeuwen FE. Residential traffic density and cancer incidence in Amsterdam, 1989-1997.
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ABSTRACT

Objective
To examine the association between cancer incidence in 1989-97 in Amsterdam and residential traffic intensity.
Methods
We linked data on the daily traffic intensity for individual addresses along the main roads with the population-based regional cancer registry. Information on smoking habits was derived from a smoking survey.
Results
During 1989-1997, 27 157 cancer cases were diagnosed in Amsterdam residents. Using the age group- and sex-specific cancer incidence in the population not residing along the main roads as a reference, the standardised incidence ratio (SIR) of the population residing along the main roads was 1.03, (3 384 cases), while the 95% confidence interval (CI) included unity (1.00–1.07). For most cancer sites the SIR was close to 1, except for gastrointestinal cancer in males (SIR 1.16, CI: 1.04, 1.28), cancer of the respiratory tract in females (SIR 1.13, CI: 0.97, 1.31) and haematological malignancies in adult females (SIR 1.23, CI: 1.04, 1.44). Five cases of acute lymphocytic leukaemia were diagnosed in children along the main roads (SIR 2.5, CI: 0.8, 5.9). Smoking habits did not differ between residents along the main roads and those living along other roads.
Conclusions
We found no clear evidence for an association between residence along main roads and the incidence of cancer in adults, but we cannot exclude an association with haematological malignancies in females and children.

ABBREVIATIONS USED

ALL = acute lymphocytic leukaemia; CI = confidence interval; E = expected (number); O = observed (number); OR = odds ratio; SES = socio-economic status; SIR = standardised incidence ratio; TIS = traffic intensity score

INTRODUCTION

In many urban areas road traffic is the major source of local air pollution. In a number of studies, elevated concentrations of especially black smoke and NO_2 were measured in the ambient air near traffic routes and busy streets compared to the ambient urban background.[1] Black smoke is indicative of diesel exhaust.[2] The International Agency for Research on Cancer has classified the emission of diesel engines as probably carcinogenic (2A) and the emission of gas engines as possibly carcinogenic (2B).[3]
The relation between ambient air pollution and cancer has been the subject of numerous studies in the general population or in occupationally exposed populations. In a number of studies urban air pollution was reported to be associated with (lung) cancer.[4-8] The findings on the association between cancer risk and occupational exposure to vehicle exhaust related air pollution are inconclusive, mostly due to limited exposure information and incomplete information on confounders like smoking.[9-16] Several studies have reported an increased risk for leukaemia in association with residential traffic density.[17-19] However, this was not confirmed in a large case-control study by Raaschou-Nielsen et al.,[20] and several other studies.[21-24] The role of residential traffic density in childhood leukaemia remains subject of discussion.[25-27]
In Amsterdam, traffic circulation is regulated by way of a network of designated roads. Approximately 12 percent of the addresses in Amsterdam are situated along traffic roads with more than 10 000 vehicle equivalents per day. Fisher et al. measured the largest contrasts between outdoor air concentrations in front of homes along busy and quiet streets in Amsterdam for carcinogenic compounds like benzo(a)pyrene, total polycyclic aromatic hydrocarbons and benzene.[28] Similar differences were found for the indoor air of these homes. However, the number of measurements was small. Within the urban area of Amsterdam substantial differences, up to 300 percent, exist between ambient air black smoke concentrations at road traffic measurement sites and background sites.[29]
Considering the large number of cancer cases available in the Amsterdam Cancer Registry and the unique information on residential traffic density in the city since 1986, we conducted a population-based study to examine the effect of residency along busy roads on the incidence of cancer. Because of the findings in other studies we were particularly interested in the incidence of cancer of respiratory tract (mainly lung cancer) and haematological malignancies, especially in children.

MATERIALS AND METHODS

Cancer registry

The cancer registry of the Comprehensive Cancer Centre Amsterdam ('Amsterdam Cancer Registry') is population-based since 1988 and covers the province of Noord-Holland and the larger part of Flevoland. On January 1st, 1998, the population of the region numbered 2.72 million, of which 718 000 with residence in Amsterdam. The Amsterdam Cancer Registry is part of the Netherlands Cancer Registry.[30] All malignant tumours, with the exception of basal cell carcinomas of the skin, are registered in all 20 hospitals in the region. Data from residents diagnosed in a hospital outside our region, are routinely obtained from the national registry.

Cancer registry data are extracted directly from the medical records. Apart from demographic data, data are collected on the site and morphological classification (according to the International Classification of Diseases for Oncology), stage and the primary treatment. Finally, the 4-digit postal code at the date of diagnosis is registered.
For this study all cancer cases diagnosed from 1 January 1989 through 31 December 1997 in patients residing in Amsterdam at the date of diagnosis were selected from the cancer registry. Borderline and non-invasive tumours were excluded. Kaposi's sarcomas were also excluded, because these malignancies occurred almost exclusively among the members of the gay community of Amsterdam and this community is geographically unevenly distributed over the city. Cancer cases diagnosed in 1988 could not be included in the study, because detailed address data as necessary for this study were not accessible.

Daily traffic intensity

By means of infrastructural works and other measures taken in the past decades, the traffic flows in Amsterdam are primarily through the so-called 'main road network', while the other roads are mostly used by residential traffic. Consequently, the main roads are the most busy roads of Amsterdam. Data on the daily traffic intensity of the main roads in 1986, 1991 and 1993 were obtained from the Environmental Research Institute City of Amsterdam (OMEGAM). Traffic intensity for roads not belonging to the main road network is not available. Based on actual counts or interpolations, the 24-hour numbers of passenger cars and trucks were available for all road segments of the main road network. There were 55 719 addresses along the main roads out of a total of 373 157 addresses in Amsterdam. For each address, the distance (in meters) between the road axis and the front of the house was also available. We added 5 778 main road addresses to 'other roads', because that distance was more than 50 meters. For each of the remaining 49 941 addresses a daily traffic intensity score (TIS) was calculated for each of the 3 available years, passenger cars counting for 1 and trucks, with their larger emissions, counting for 10. An address belonged to the main road network if the TIS was 10 000 or higher during at least one of the three years. For 4 077 addresses the TIS was below 10000 in all three available years. These 4 077 addresses were added to 'other roads', leaving 45 864 addresses (12.3 percent of the total number of addresses in Amsterdam), classified as 'main road addresses'. For 25 168 of these main road addresses the TIS was 20 000 or higher in at least one of the three available years.

Population data

Annual population data according to sex and 5-year age groups were obtained for each year of the study period from the Statistical Office of Amsterdam (O + S), which received its data from the population register of Amsterdam. Population data (date of birth, sex, marital status, country of birth, address, etc.) in the Netherlands are not census-derived, but recorded on a day-to-day basis by the municipal population registers and include detailed address data. We obtained data for 'main roads' (TIS ≥ 10000), 'other roads', as well as separate data for main road addresses with 10 000 ≤

TIS < 20 000 and TIS ≥ 20 000, respectively. The average population with residence along main roads was 76000 inhabitants, that is 35 000 with 10 000 ≤ TIS < 20 000 and 41 000 with TIS ≥ 20 000, while the average population size along other roads was 637 000. There were on average 8 700 children with residence along main roads (4200 with 10 000 ≤ TIS < 20 000 and 4500 with TIS ≥ 20 000), while on average 96000 children resided along other roads.

Address according to population register

A full postal code in the Netherlands consists of 4 digits followed by 2 letters. The combination of the full postal code and the number of the house can identify each individual address. Because the 4 digit postal code as available in the cancer registry was insufficiently accurate for defining whether a patient was living along a main road or not, supplementary address data were requested from the Amsterdam population register. By means of record linkage (using the date of birth, gender and 4 letters of the family name) of the cancer registry data and a data file containing address data of all present and former (since 1989) Amsterdam residents, supplementary address data (full postal code and the number of the house) were added to the cancer registry data, ignoring the original postal codes as available in the cancer registry. However, in 89 percent of the cases the postal code in the cancer registry equalled the postal code in the population register. All cancer cases for which computerized linkage was unsuccessful were extensively checked by hand. For all patients still alive and residing in Amsterdam we used the address data at April 1st 1998, when the data file of the population register was generated. For patients who had died or moved away from Amsterdam, we used the address data at the date of death or the last address in Amsterdam, respectively. Finally, cancer registry data were linked to the main road addresses (TIS ≥ 10 000), as previously defined on the basis of the daily traffic density, thus separating cancer cases residing along main roads and along other roads. Subsequently in this article, 'main road' cancer cases are cases with residence along the main road network (TIS ≥ 10 000) at April 1st 1998, at the date of death or at the date of departure from Amsterdam. All other cancer cases are cases with residence along 'other roads'.

Survey on smoking habits

Smoking is an important potential confounder when examining the association between traffic density and cancer. As information on smoking was not available in the cancer registry we conducted a population-based survey to see whether smoking habits differed between residents along main roads and other roads. A total of 5 000 addresses in Amsterdam were randomly selected from the file made available by the Population Register of Amsterdam. Two thousand five hundred addresses were along the main roads of Amsterdam. The other 2 500 were along other roads. In order to obtain a population sample that could easily be compared to cancer patients, the selection of addresses was stratified according to the age and sex distribution of the latter group. One thousand extra addresses of both categories were kept standby. The selected addresses were approached by telephone, followed by a telephone interview with the main occupant or his/her partner. Children were not interviewed. Prior to the

interview a letter was sent to all addresses by the Municipal Health Service Amsterdam, introducing the telephone interview. It included questions on the present and past smoking status, present (or past) number of packs smoked weekly, the type(s) of tobacco (cigars, cigarillos, [hand-rolled] cigarettes, pipe-tobacco), starting age and time passed since giving up smoking, as well as some demographic items like age, sex, duration of residence at the present address, education and profession. The survey was performed in January - February 2000 by NIPO, a market research institute with ample experience regarding telephone interviews. NIPO used Computer Assisted Telephone Interviewing, in which the questions appear on the screen of the interviewer and the answers are entered directly into the computer.

Data analysis

We calculated 5-year age group- and sex-specific cancer incidence rates for total Amsterdam, as well as for inhabitants not residing along main roads. Using the latter incidence rates as a reference and the distribution according to 5-year age group and sex of residents along the main roads of Amsterdam, we calculated expected numbers (E) of cancer for residents along main roads. We calculated separate expected numbers for main roads with 10 000 ≤ TIS <20 000 and TIS ≥20 000 as well. Expected numbers were compared with the observed numbers (O) and standardised incidence ratios (SIR) with corresponding 95 percent confidence intervals based on the Poisson distribution of O were calculated using STATA 7.0 for Windows (STATA Corporation, College Station, Texas, USA).

Table 1. Main characteristics of cancer patients in Amsterdam according to residency, 1989-1997

parameter	*residency*					
	along main roads		*along other roads**		*total*	
	n	*%*	*n*	*%*		%
age						
< 45	229	7	2 259	10	2 498	9
45-59	475	14	4 161	18	4 636	17
60-74	1 220	36	9 206	39	10 426	38
75 or older	1 450	43	8 147	34	9 597	35
sex						
male	1 630	48	11 976	50	13 606	50
female	1 754	52	11 797	50	13 551	50
total	3 384		23 773		27 157	

* including 225 cases with unknown address

RESULTS

Cancer incidence

In 1989-1997 a total of 27 157 cancer cases (13 606 males, 13 551 females) were diagnosed among inhabitants of Amsterdam. Table 1 shows that a total of 3 384 cancer patients (12.4 percent of the total number) had residence along the main roads of Amsterdam, 1630 males and 1754 females. 23 548 cancers were diagnosed in patients

Table 2. Observed and expected number of cancers in subjects residing along the main roads of Amsterdam, 1989-1997 (reference population: remaining Amsterdam)

cancer site		*total*				*10 000 ≤ TIS < 20 000*				*TIS ≥20 000*			
ICD-10 code	*description*	*O*	*E*	*SIR*	*95% CI*	*O*	*E*	*SIR*	*95% CI*	*O*	*E*	*SIR*	*95% CI*
C00-14	Head & neck	63	77.7	0.81	0.62, 1.04	39	38.5	1.01	0.72, 1.38	24	39.2	0.61	0.39, 0.91*
	- males	38	48.9	0.78	0.55, 1.07	22	23.8	0.92	0.58, 1.40	16	25.1	0.64	0.36, 1.04
	- females	25	28.8	0.87	0.56, 1.28	17	14.7	1.16	0.67, 1.85	8	14.2	0.57	0.24, 1.11
C15-26	Gastrointestinal tract	795	739.9	1.07	1.00, 1.15	423	389.7	1.09	0.98, 1.19	372	350.2	1.06	0.96, 1.18
	- males	378	326.4	1.16	1.04, 1.28*	207	168.7	1.23	1.07, 1.41*	171	157.8	1.08	0.93, 1.26
	- females	417	413.5	1.01	0.91, 1.11	216	221.1	0.98	0.85, 1.12	201	192.4	1.04	0.91, 1.20
C30-34	Respiratory system	576	552.7	1.04	0.96, 1.13	329	284.3	1.16	1.04, 1.29*	247	268.4	0.92	0.81, 1.04
	- males	400	396.9	1.01	0.91, 1.11	226	204.6	1.10	0.97, 1.26	174	192.3	0.90	0.78, 1.05
	- females	176	155.7	1.13	0.97, 1.31	103	79.6	1.29	1.06, 1.57*	73	76.1	0.96	0.75, 1.21
C50	Female breast	459	460.9	1.00	0.91, 1.09	228	232.8	0.98	0.86, 1.12	231	228.0	1.01	0.89, 1.15
C51-58	Female genital organs	202	201.9	1.00	0.87, 1.15	109	102.3	1.07	0.87, 1.29	93	99.6	0.93	0.75, 1.14
C61	Prostate	289	289.5	1.00	0.89, 1.12	168	153.4	1.10	0.94, 1.27	121	136.1	0.89	0.74, 1.06
C65-68	Bladder/oth. ur. tract	151	147.8	1.05	0.87, 1.20	90	77.6	1.16	0.93, 1.43	61	70.2	0.87	0.66, 1.12
	- males	105	105.1	1.00	0.82, 1.21	61	54.7	1.11	0.85, 1.43	44	50.4	0.87	0.63, 1.17
	- females	46	42.7	1.08	0.79, 1.44	29	22.9	1.27	0.85, 1.82	17	19.8	0.86	0.50, 1.37
C81-95	Haematological mal.	275	249.1	1.10	0.98, 1.24	146	126.6	1.15	0.97, 1.36	129	122.5	1.05	0.88, 1.25
	- adult males	122	124.7	0.98	0.81, 1.17	57	61.7	0.92	0.70, 1.20	65	63.0	1.03	0.80, 1.32
	- adult females	148	120.7	1.23	1.04, 1.44*	89	63.2	1.41	1.13, 1.73*	59	57.5	1.03	0.78, 1.32
	- children (< 15 years)	5	3.7	1.35	0.44, 3.15	-	1.8	0.00	0.00, 2.05	5	1.9	2.63	0.85, 6.14
C37-49,	Other sites ‡	574	555.5	1.03	0.95, 1.12	315	283.9	1.11	0.99, 1.24	259	271.6	0.95	0.84, 1.08
C60, C62-63,	- males	293	281.2	1.04	0.93, 1.17	162	141.8	1.14	0.97, 1.33	131	139.5	0.94	0.79, 1.11
C69-80	- females	281	274.3	1.02	0.91, 1.15	153	142.2	1.08	0.91, 1.26	128	132.2	0.97	0.81, 1.15
C00-95	Total ‡	3 384	3 275.0	1.03	1.00, 1.07	1 847	1 689.2	1.09	1.04, 1.14*	1 537	1 585.8	0.97	0.92, 1.02
	- adult males	1 622	1 570.0	1.03	0.98, 1.08	902	807.3	1.12	1.05, 1.19*	720	762.7	0.94	0.88, 1.02
	- adult females	1 752	1 696.4	1.03	0.98, 1.08	943	877.7	1.07	1.01, 1.15*	809	818.7	0.99	0.92, 1.06
	- children (< 15 years)	10	8.7	1.16	0.55, 2.11	2	4.2	0.48	0.06, 1.72	8	4.5	1.79	0.77, 3.50

* p<0.05

‡ excluding Kaposi's sarcoma (C46)

CI = confidence interval; E = expected number; O = observed number; SIR = standardised incidence ratio; TIS = traffic intensity score

residing along other roads. Of 225 cases (0.9 percent) address data were insufficiently accurate to determine whether a case lived along a main road or not. On average patients with residence along the main roads were somewhat older than patients living elsewhere in Amsterdam. Over 70 percent of the patients were 60 years or older, while only 9 percent were below the age of 45.

The age-standardized cancer incidence rate (European standardized rate[31]) for total Amsterdam was 470.7 per 100 000 males and 355.1 per 100 000 females, which was 3 and 7 percent above the national average, respectively. Compared to the national average, rates for total Amsterdam in males were increased for cancer of the oral cavity, pharynx, liver, mesothelioma, urinary tract and non-Hodgkin's lymphoma. Colorectal cancer, gallbladder, skin and testicular cancer were well below the national average. Compared to the national average, the rates for total Amsterdam in females were increased for smoking-related cancers (head & neck, lung, bladder), as well as for cervical cancer and non-Hodgkin's lymphoma. The female rates for cancer of the gallbladder and the skin, as well as leukaemia were below the national average. The incidence rates for the population not residing along the main roads were almost equal to the incidence rates for total Amsterdam.

Using the age group- and sex-specific cancer incidence rates for 1989-1997 in the population not residing along the main roads as a reference, expected numbers of cancer cases in the population along the main roads were close to the observed numbers (table 2). For both sexes combined, the standardized incidence ratio (SIR) for total cancer was 1.03 (95 percent confidence interval [CI]: 1.00, 1.07). For cancer of the respiratory system, we calculated a SIR of 1.01 (males) and 1.13 (females, 95 percent CI: 0.97, 1.31). The SIR of the other specific cancer sites was close to 1, with the exception of gastrointestinal tract in males (SIR 1.16, 95 percent CI: 1.04, 1.28) and haematological malignancies in children (SIR 1.35, 95 percent CI: 0.44, 3.15) and adult females (SIR 1.23, 95 percent CI: 1.04, 1.44). The latter increase was mainly caused by an increased number of cases of non-Hodgkin's lymphoma (SIR 1.23, 95 percent CI: 0.97, 1.54) and multiple myeloma (SIR 1.33, 95 percent CI: 0.90, 1.90) and a statistically significantly increased number of cases of myeloid leukaemia (SIR 1.60, 95 percent CI: 1.01, 2.40). In both sexes combined, there were 69 adult cases of leukaemia (SIR 1.19, 95 percent CI 0.93, 1.51), of which 29 cases of lymphoid leukaemia (SIR 1.07, 95 percent CI: 0.72, 1.54) and 40 cases of myeloid leukaemia (SIR 1.29, 95 percent CI: 0.93, 1.76).

The total number of 10 cancer cases in children with residence along the main roads was close to an expected number of 8.7 cases. All 5 children up to the age of fifteen with haematological malignancies were diagnosed with acute lymphocytic leukaemia [ALL] (SIR 2.5, 95 percent CI: 0.8, 5.9)

In residents along the busiest main roads (TIS ≥ 20 000), the SIR for total cancer was 0.97 (0.94 for males and 0.99 for females), while in residents along less busy main roads (10 000 ≤ TIS < 20 000) the SIR for all cancers combined was slightly increased (SIR 1.09; 95 CI: 1.04, 1.14). This latter increase was mainly caused by relatively high numbers of cancer of the gastrointestinal tract in males (SIR 1.23; 95 CI: 1.07, 1.41) as well as cancers of the respiratory tract (SIR 1.29; 95 CI: 1.06, 1.57) and haematological malignancies (SIR 1.40; 95 CI: 1.12, 1.72) in females.

All 5 children with ALL had residence along the busiest main roads (SIR 4.9, 95 percent CI: 1.6, 11.4).

Table 3. Main characteristics and smoking habits of participants of a smoking survey in Amsterdam, according to residency

characteristics	*residency along main roads*		*residency along other roads*		*total*	
	n	*%*	*n*	*%*	*n*	*%*
age						
< 45	329	24	193	14	522	19
45-59	236	18	202	15	438	16
60-74	402	30	428	32	830	31
75 or older	377	28	523	39	900	33
unknown	2	0	1	0	3	0
sex						
male	689	51	688	51	1 377	51
female	657	49	659	49	1 316	49
socio-economic status						
A (high)	345	26	219	16	564	21
B	243	18	214	16	457	17
C	520	39	596	44	1 116	41
D (low)	238	18	318	24	556	21
duration of residency at present address						
5 years or less	325	24	276	20	601	22
6-10 years	186	14	181	13	367	14
11-20 years	271	20	280	21	551	20
21-30 years	184	14	180	13	364	14
> 30 years	374	28	427	32	801	30
unknown	6	0	3	0	9	0
smoking history						
present smoker	398	30	394	29	792	29
past smoker	556	41	560	42	1 116	41
never smoker	392	29	393	29	785	29
pack-years smoked						
< 1	434	32	434	32	868	32
1-10	300	22	302	22	602	22
11-20	196	15	182	14	378	14
21-30	162	12	153	11	315	12
31-40	89	7	104	8	193	7
41-50	79	6	75	6	154	6
> 50	86	6	97	7	183	7
total	1 346		1 347		2 693	

Smoking survey

The final survey on smoking habits comprised 5 022 subjects, with whom a total of 2693 successful interviews equally divided over both subsamples were realized (table 3). The response rate was 53.6 percent for both subsamples combined. On average, participants living along main roads of Amsterdam were younger and had a higher socio-economic status (SES) than the participants living elsewhere in Amsterdam (table 3). Sixty-two percent of the subjects residing along main roads had been living there for at least 10 years and 42 percent for at least 20 years. For subjects with residency along other roads these figures were 66 and 45 percent, respectively. For subjects of

45 years or older (both subsamples combined) the figures were 75 and 53 percent, respectively (data not shown). The smoking history -present, past or never smoker- did not differ between residents along main roads and residents elsewhere in Amsterdam. Also, the distribution of the number of pack-years of cigarettes smoked did not differ between the two population samples. In a multivariate logistic regression (adjusted for age, sex and SES) residence along the main roads was not associated with smoking history (OR 0.9, 95 percent CI 0.8-1.1).

DISCUSSION

During 1989-1997, the overall incidence of cancer among inhabitants of Amsterdam residing along main roads was close to that of the remaining population of Amsterdam. We found an increased incidence of cancer of the gastrointestinal tract in males as well as increased rates for haematological malignancies in adult females, cancer of the respiratory system in females and haematological malignancies in children. However, the 95 percent confidence intervals of the relative risks of the latter two diagnoses included unity. For cancer of the respiratory tract and haematological malignancies in females we found no increase among residents along the busiest main roads, while for cancer of the gastrointestinal tract in males the increase among residents along the busiest main roads was less than among residents along less busy main roads, which argues against a causal association.

All types of haematological malignancies combined occurred more often among children and females living along the main roads than among residents of the remaining city of Amsterdam. This was caused by an increase of acute lymphocytic leukaemia in children (SIR 2.8) and an increase of non-Hodgkin's lymphoma (SIR 1.23 versus SIR males 0.99), multiple myeloma (SIR 1.33 versus SIR males 0.79) and myeloid leukaemia in adult females (SIR 1.60 versus SIR males 1.03). The male/female differences in excess risk in lymphoma, multiple myeloma and myeloid leukaemia, as well as the absence of an increased risk of haematological malignancies in females with residence along the busiest roads (SIR 1.03), render a causal association with residence along the main roads less likely. The number of cases of childhood leukaemia was small in our study, but we found a statistically significantly increased risk of ALL in children with residence along the busiest roads. It must be pointed out, however, that the confidence interval surrounding the risk estimate was wide and that the risk increase relates to a subgroup analysis which was done as a result of our observation of increased risk for haematological malignancies. In three other studies elevated risks for leukaemia were also reported.17-19 Although the SIR for childhood ALL in our study was increased, the public health implications are relatively small. If the association between traffic density and childhood ALL were causal, we estimate that, based on our results, 1 excess case of ALL would occur every 3 years among children with residency along the main roads in Amsterdam.

The incidence of cancer of the gastrointestinal tract in males residing along main roads was slightly increased (SIR 1.16). However, a causal association between urban air pollution and cancer of the gastrointestinal tract is not very plausible from a biological perspective. The lack of a dose-response relation (SIR in residents along the busiest

main roads 1.08) does not support a causal association either. More likely, this result is a chance finding attributable to the multiple comparisons in our analysis.
Since tobacco smoke and ambient air pollution contain many identical toxic compounds, smoking is an important potential confounder in this study. Although the populations compared are quite large and one would not a priori expect differences in the smoking habits of residents along main roads and other roads, a drawback of our study is the lack of information on individual smoking histories. We did, however, obtain information on the smoking habits of large random samples of the populations involved. The results of our survey showed almost identical smoking histories among residents living along the main roads and the population residing elsewhere in Amsterdam.
We observed a slightly increased incidence of cancer of the respiratory tract in females (SIR 1.13), but not in males. Although this result was not statistically significant, we cannot exclude a weak association between residency along main roads and cancer of the respiratory tract in females, taking into account the fact that women used to be more often at home than men. Especially in the past, the proportion of employed women in the Netherlands was rather low. Therefore, the total exposure to traffic-related air pollution may have been greater for women than for men. However, our observation that no increased incidence was present among female residents along the busiest main roads and that the distribution according to morphological type of cancer of the respiratory tract (data not shown) was similar in residents along main roads and other roads, both in males and in females, do not support a possible association.
At first sight, our finding of a slightly increased cancer incidence among residents along less busy roads (SIR 1.09), while there was no increase among residents along the busiest roads (SIR 0.97) does not appear to support a causal relation between cancer and main roads. However, because of the municipal policy for sound insulation, the houses along the busiest main roads were better insulated and we cannot exclude the possibility that this insulation policy may have led to lower levels of pollutants in the houses along the busiest roads in comparison to less busy roads. We did not perform separate analyses for trucks and cars, although trucks may have been the main source of traffic-related air pollution, as the numbers of trucks and cars were highly correlated (correlation coefficients were as high as 0.97, 0.87 and 0.96 in 1986, 1991 and 1993, respectively).
A drawback of the study is the possibility of non-differential misclassification, since people may have moved from main roads to other roads and vice versa. However, the smoking survey showed comparable residence times between the two groups. Moreover, nearly two thirds of inhabitants had not changed their residency in the last 10 years. The record linkage of cancer registry data to the data from the Amsterdam Population Register showed that the 4-digit postal code at the date of diagnosis in the cancer registry was equal to the last known address in 89 percent of the cases. Nevertheless, some random misclassification is likely to be present in this study, causing an attenuation of the true risk estimates towards unity.
Less than 1 percent of the cancer cases could not be found in the Amsterdam Population Register. Among these, people born outside the Netherlands were relatively common. Possibly, they were residing in Amsterdam illegally, or they were living temporarily with relatives in Amsterdam because of cancer treatment in one of the Amsterdam

hospitals. Because there is no reason to assume that the unclassifiable cases would have had residence along the main roads more often than known cases, it is unlikely that the very low proportion of unclassifiable cases has influenced our results.
Finally, the differences in SES between residents along the main roads and other roads may have slightly influenced our results. According to the Amsterdam Bureau for Research and Statistics, residents along main roads had somewhat higher levels of education, 43 percent 'high' versus 39 percent 'high' among residents along other roads. Family incomes were almost equal, 12 percent 'high' among residents along main roads and 13 percent 'high' among residents along other roads. Among participants of the smoking survey, we also found a higher percentage of residents along the main roads in the highest SES category (26 percent versus 16 percent). However, this difference was most pronounced in younger participants. In participants of the smoking survey over the age of 50, the difference in SES was much smaller, 14 percent category A in residents along main roads versus 10 percent in residents along other roads. As the majority of cancer patients is also older than 50, we conclude that SES is unlikely to have influenced our results substantially.
In conclusion, our large population-based study does not support the association between traffic related air pollution and cancer incidence in adults as observed in some studies. However, an increased risk of ALL among children along the busiest roads was observed and this possible association should be the subject of further research.

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4

CANCER SURVIVAL

4.1 Stage-specific survival of epithelial cancers in North-Holland/Flevoland, the Netherlands.

Visser O, Van Leeuwen FE. Stage-specific survival of epithelial cancers in North-Holland/Flevoland, the Netherlands.
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ABSTRACT

While stage is the most important factor for determining cancer survival, population-based survival data according to stage are rarely presented. We present such data for a large population diagnosed with cancer in the area covered by the Amsterdam Cancer Registry in 1989-2001 (n=108 251). Cases were grouped according to the TNM-Classification. For all sites, a close relation between stage at diagnosis and survival was observed. The stage-specific 5-year relative survival rate (RSR) ranged from close to 100% for stage I carcinoma of the salivary glands, thyroid, colon/rectum, skin, breast, female genitals, prostate and urethra to ≤ 1% for stage IV carcinoma of the oesophagus, stomach, liver, gallbladder, pancreas and lung. Between 1989-1991 and 1999-2001, we observed an increase of the stage-specific RSR for carcinoma of colon/rectum (stages II-IV), lung (stages I-II), breast (stages I-III) and prostate (stages II-IV). Changes in diagnostic (breast, prostate) and staging procedures (lung), surgery (rectum, prostate) and adjuvant treatment (breast, colon) are likely to have contributed to this increase.

1. INTRODUCTION

Information on the prognosis of cancer patients is important for both patients and their clinicians. From the EUROCARE-3 study, age- and site-specific survival rates are available for many European countries [1]. However, the prognosis of a cancer patient is also influenced by many other factors, such as morphological type, treatment and co-morbidity [2,3]. For epithelial cancers, stage is the most important factor and most survival differences between populations can be explained by differences in stage distribution [4,5]. Moreover, stage-specific survival rates are essential for the interpretation of differences in survival rates between sexes or changes in the overall survival rates over time, as the overall survival will change as a result of changes in stage distribution. Unfortunately, stage-specific survival is unavailable in the majority of the European cancer registries, which hampers the comparison of survival rates between registries and the explanation of survival changes over time.
The nation-wide Netherlands Cancer Registry collects stage information for all relevant cancer sites and, consequently, is uniquely positioned to examine population-based survival according to stage. In this paper, we present stage-specific survival rates for all major epithelial cancers as well as melanoma skin cancer, based on a very large population-based cohort of cancer patients in the north-western part of the Netherlands.

2. PATIENTS AND METHODS

2.1 The Amsterdam Cancer Registry

The Amsterdam Cancer Registry (ACR), is a regional, population-based cancer registry with complete regional coverage since January 1st, 1988. The region of the ACR covers the major part of two out of twelve provinces of the Netherlands: North-Holland and Flevoland. Its population numbered 2.84 million on December 31st, 2001, approximately 17% of the total population of the Netherlands. The ACR is part of the nation-wide Netherlands Cancer Registry, whose data are included in Cancer Incidence in Five Continents as of volume VII [6,7]. Cases diagnosed in a hospital outside the ACR region but with residence in the ACR region, are routinely obtained from the national registry and included in the regional registry.
The information for the registry is extracted from the medical records by registration clerks. Apart from demographic data, data are collected on tumour site and morphological classification (according to the International Classification of Diseases for Oncology), stage of the tumour and primary treatment of the patients. For the stage of the tumour, TNM is registered whenever applicable. We used the 4th edition for cases diagnosed in 1989-92, the 2nd revision of the 4th edition in 1993-98 and the 5th edition in 1999-2001 [8,9].

2.2 Study population

For this study, we selected cancer sites included in the 5th edition of the TNM Classification [9]. Cancer sites with mainly non-epithelial cancers (bone, soft tissue, eye) were excluded. Skin melanoma was included.

Stage grouping was according to the 5th edition of the TNM-classification, based on a combination of clinical TNM (cTNM) and pathological TNM (pTNM). If pTNM was available (61% of the cases) we used pTNM-data, otherwise cTNM-data were used. In case of small numbers, stages were grouped together.
The TNM-classification for carcinoma of the small intestines was not available until the 2nd revision of the 4th edition. We converted the extent of disease as registered in 1989-92 to TNM-stage as follows: localised=stage I, direct extension=stage II, regional lymph node metastasis=stage III, distant metastasis=stage IV.
Between January 1st, 1989 and December 31st, 2001 a total of 130 619 first invasive cancers were registered. After exclusion of sites with mainly non-epithelial cancers and sites for which TNM was not applicable, 108 251 cancers remained (table 1).

2.3 Follow-up

For patients with residence in the ACR region and diagnosed in 1989-97, the vital status was updated by linking electronic files with deceased persons to the cancer registry. These files were made available in 1999/2000 by 54 municipal population registers (covering 90% of the population of the region) out of a total of 74 registers in the region. The files included all deceased residents (irrespective of cause of death) of those municipalities, generally covering the period 1989-99. Active follow-up was performed in the hospitals for all patients with residence in the remaining 20 municipalities and in case the datafile made available by the municipal population register covered only a part of the period 1989-99. In case of missing data in the hospital, the municipal population registers were asked for the date of death of individual patients.
In September 2003, the vital status of all patients (diagnosed 1989-2001) still alive at last follow-up was updated by linkage to the electronic death register of the Central Bureau for Genealogy (CBG), which contains all deceased residents of the Netherlands as of October 1st 1994. This electronic register is updated on a daily basis with data from all municipal population registers in the Netherlands. Patients who probably died before October 1st 1994 according to hospital information, but with unknown date of death, were checked in the personal record card register of the CBG which contains all Dutch residents who died before October 1st 1994. Finally, all patients not known by CBG were assumed to be alive at 1 September 2003, one week before record linkage with the electronic death register was performed.
Checks on the vital status of patients assumed to be alive at 1 September 2003 were performed in the hospitals for all patients with metastatic disease at diagnosis, patients over 95 years of age in 2003 and patients with cancer of the oesophagus, stomach, liver, gallbladder, bile ducts, pancreas, and lung. This procedure revealed that the number of patients assumed to be alive after record-linkage but who turned out to have died according to hospital information, was negligible. Overall, missing dates of death are estimated to be well below 0.5%.

2.4 Statistical analysis

Because the cause of death is not available in the population registers and consequently not complete in our data set, and because linkage with the cause of death registration of Statistics Netherlands is not possible because of privacy regulations, we

were unable to calculate disease specific survival. As an alternative, we calculated relative survival and 95% confidence intervals using STATA 7.0 (StataCorp. Stata Statistical Software: Release 7.0. College Station, TX: Stata Corporation) with software written by Dickman and colleagues [10], based on a computer package developed by Hakulinen and Abeywickrama [11]. This method corrects observed survival for expected mortality according to annual life tables of the general population. We used national age-, sex- and calendar year-specific life tables from Statistics Netherlands [12].

Table 1. Invasive cancers according to TNM-stage, North-Holland/Flevoland, the Netherlands, 1989-2001 (second and subsequent cancers excluded)

	No. of cases	*TNM-stage*					*non-epith. cancers**	*no microsc. confirmation*
		I	*II*	*III*	*IV*	*Unknown*		
Lip/oral cavity	1 654	40%	16%	10%	29%	3%	1%	0%
Pharynx	889	5%	10%	21%	63%	1%	1%	0%
Larynx	1 353	39%	25%	11%	23%	1%	1%	0%
Maxillary sinus	66	3%	6%	26%	58%	0%	5%	3%
Salivary glands	232	38%	11%	6%	22%	11%	12%	0%
Thyroid gland	665	43%	19%	19%	17%	2%	0%	0%
Oesophagus	2 014	4%	12%	19%	28%	36%	0%	1%
Stomach	4 472	15%	11%	17%	36%	16%	2%	2%
Small intestine	305	5%	16%	12%	17%	4%	43%	4%
Colon/rectum	15 685	17%	31%	25%	20%	3%	1%	2%
Anal canal	238	13%	40%	25%	5%	14%	3%	1%
Liver	581	1%	12%	14%	39%	16%	5%	13%
Gallbladder	452	7%	11%	15%	47%	9%	0%	12%
Extrahep. bile ducts	834	5%	5%	7%	29%	18%	1%	35%
Pancreas	3 185	10%	6%	7%	38%	5%	1%	33%
Lung	17 448	17%	4%	35%	32%	4%	1%	5%
Skin**, non-melanoma	4 987	63%	11%	2%	0%	20%	3%	0%
Skin, melanoma ***	4 718	53%	28%	13%	1%	4%		
Breast	21 121	34%	50%	8%	6%	2%	0%	1%
Vulva****	439	30%	31%	20%	12%	6%	1%	0%
Vagina	99	25%	18%	16%	21%	7%	12%	0%
Cervix uteri	1 835	51%	17%	22%	7%	2%	0%	0%
Corpus uteri	2 649	70%	8%	7%	4%	2%	8%	0%
Ovary	2 438	20%	7%	44%	17%	2%	8%	2%
Penis****	177	47%	21%	13%	3%	15%	0%	1%
Prostate	12 131	4%	49%	15%	26%	4%	0%	2%
Kidney	2 638	9%	32%	18%	23%	1%	3%	13%
Renal pelvis/ureter	434	28%	13%	23%	26%	7%	0%	3%
Bladder	4 471	45%	24%	12%	14%	3%	1%	1%
Urethra	41	22%	29%	12%	20%	15%	2%	0%
TOTAL	108251	26%	27%	18%	19%	5%	1%	3%

* mainly carcinoid tumours of the lung and gastrointestinal tract (appendix, small intestines), mixed tumours of the female genital organs and salivary glands, leiomyosarcoma of the corpus uteri, as well as germ cell and stromal tumours of the ovaries

** including scrotum

*** including melanoma of vulva (n=25), penis (n=1) and scrotum (n=2)

**** excluding melanoma

3. RESULTS

Out of a total of 108 251 patients with a primary cancer of one of the selected tumour sites (table 1), TNM-stage was available for 95% of the cases (98 210 epithelial cancers as well as 4 718 skin melanomas). 1 554 non-epithelial cancers (other than skin melanoma) of the selected tumour sites were registered (1% of the cases). A total of 3769 cancers (3%) were not microscopically confirmed, mostly cancers of the pancreas (1043 cases) and the lung (925 cases). The highest percentage of non-microscopically confirmed tumours was observed for cancers of the extrahepatic bile ducts (35%, 293 cases).

Stage I was the most registered stage for carcinoma of the lip/oral cavity, larynx, salivary glands, thyroid, skin, uterus, penis and bladder (table 1). For carcinoma of the pharynx, maxillary sinus and the digestive organs (small intestines, colon/rectum and anal canal excluded) stage IV was the most registered stage. The proportion of unknown stage was particularly high for oesophageal (36%) and skin (20%) carcinoma, mostly due to an unknown T-category.

Figures 1 to 5 show a clear relation between stage at diagnosis and the relative survival rate (RSR) for all cancer sites: a relatively high RSR in early stages and low RSRs in advanced or metastatic disease. The 5-year RSRs were almost equal for stage I and II pharyngeal carcinoma (69% and 70%, respectively), stage I and II thyroid carcinoma (99% and 98%, respectively) and stage II and III prostate carcinoma (91% and 88%, respectively). For carcinoma of the vagina and the penis the 5-year RSR was slightly higher in stage II than in stage I, but the 95% confidence intervals largely overlapped.

For stage I carcinomas, the 5-year RSR was generally between 80 and 100%. The risk of dying was almost equal to the general population risk for patients with stage I carcinoma of the salivary glands, thyroid, colon/rectum, skin, breast, female genital organs and urethra. For prostate carcinoma this figure was even above 100%. The 5-year RSR was relatively low for stage I lung carcinoma (62% and 35% for stages Ia and Ib, respectively). The lowest RSR of stage I carcinoma was observed for pancreas (15%).

For the most frequent cancer sites (breast, lung, colon/rectum, prostate), 1-year RSRs for stage IV disease were observed of 61%, 13%, 33% and 86%, respectively. For many sites, the 5-year RSR for stage IV disease was ≤ 1% (oesophagus, stomach, liver, gallbladder, pancreas, lung), but relatively high rates were observed for carcinoma of the lip/oral cavity (36%), pharynx (31%), larynx (44%) and prostate (31%). The 5-year RSR for stage IV breast carcinoma was also relatively high (17%).

Survival of cases with an unknown stage was close to stage I or stage II disease for cancers of the lip/oral cavity, skin, breast, vulva and penis, because these cases were mostly localized with an unknown T-category. For most other sites, survival of cases with unknown stage was intermediate to stage III and IV, because of the absence of apparent distant metastases.

In general, the variation in the stage-specific RSRs 5 years after diagnosis exceeded the variation in stage-specific RSRs 1 year after diagnosis. For example, the absolute differences in RSRs between stage I and stage IV breast cancer were 38% 1 year after diagnosis and 80% 5 years after diagnosis. For stage I and IV prostate carcinoma these figures are 17% and 68%, respectively.

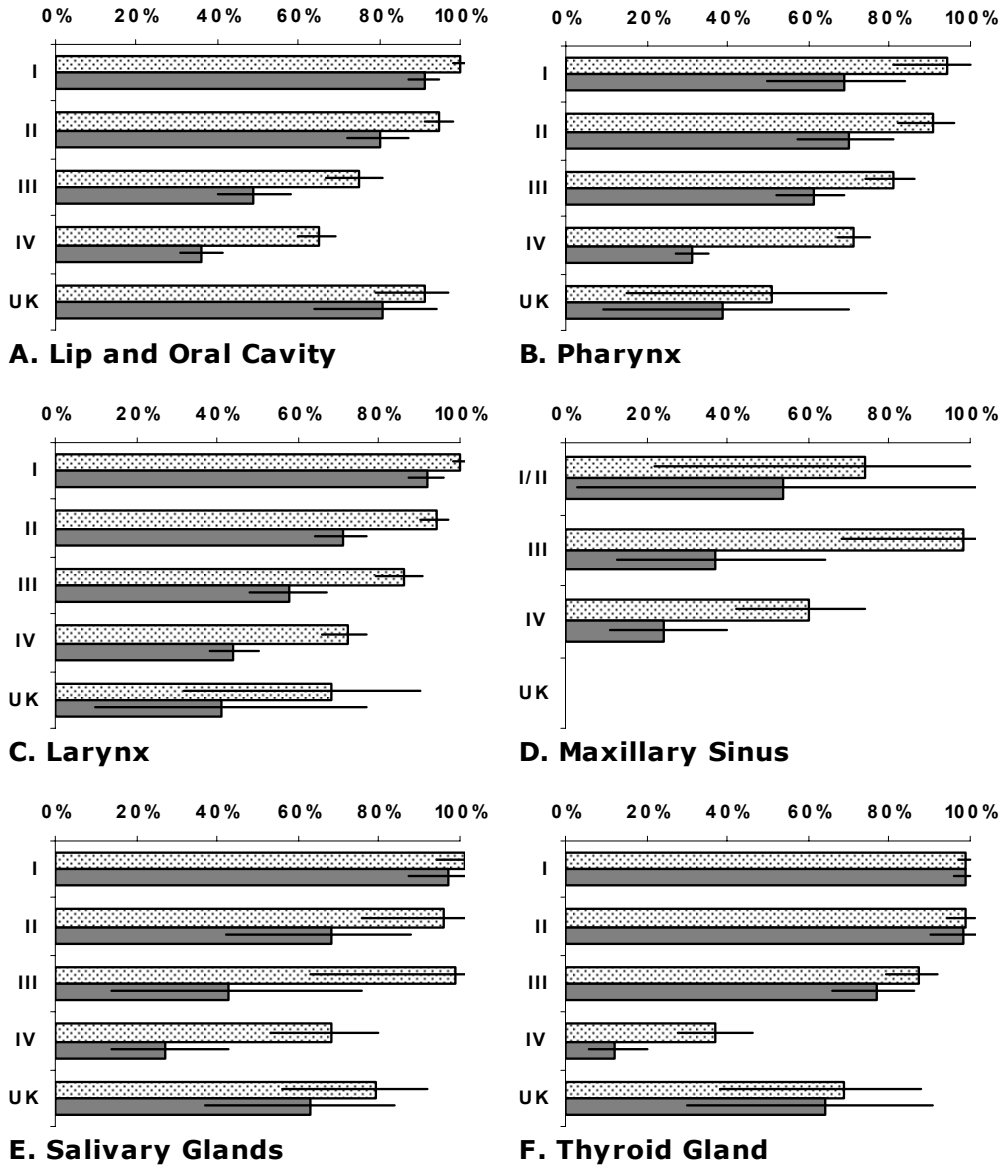

Figure 1. One-year (⊡) and five-year (■) relative survival rates of patients diagnosed with head & neck cancer according to TNM-stage, North-Holland/Flevoland, the Netherlands, 1989-2001 (UK=unknown). Lines represent 95% confidence intervals.

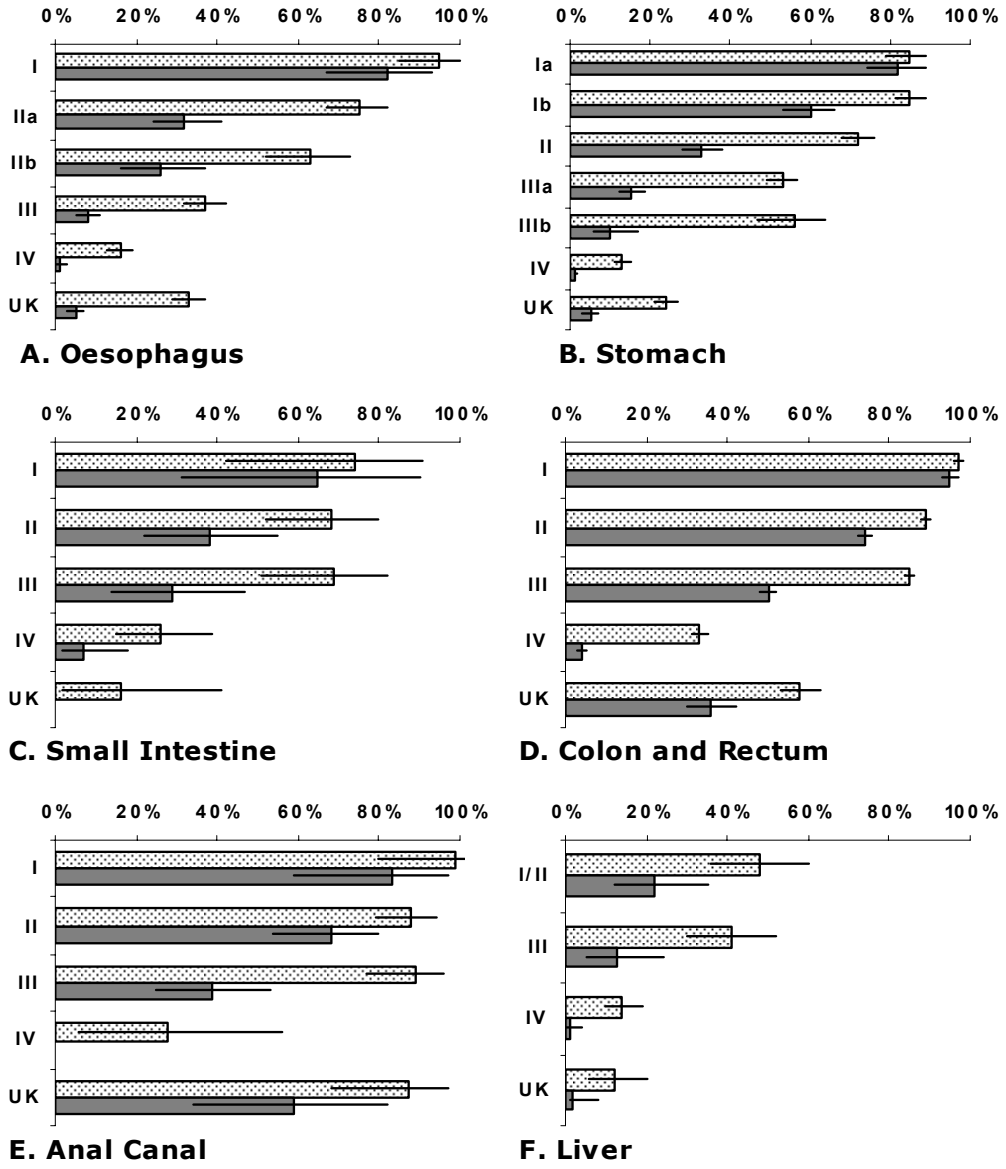

Figure 2. One-year (⊡) and five-year (■) relative survival rates of patients diagnosed with gastro-intestinal cancer according to TNM-stage, North-Holland/Flevoland, the Netherlands, 1989-2001 (UK=unknown). Lines represent 95% confidence intervals.

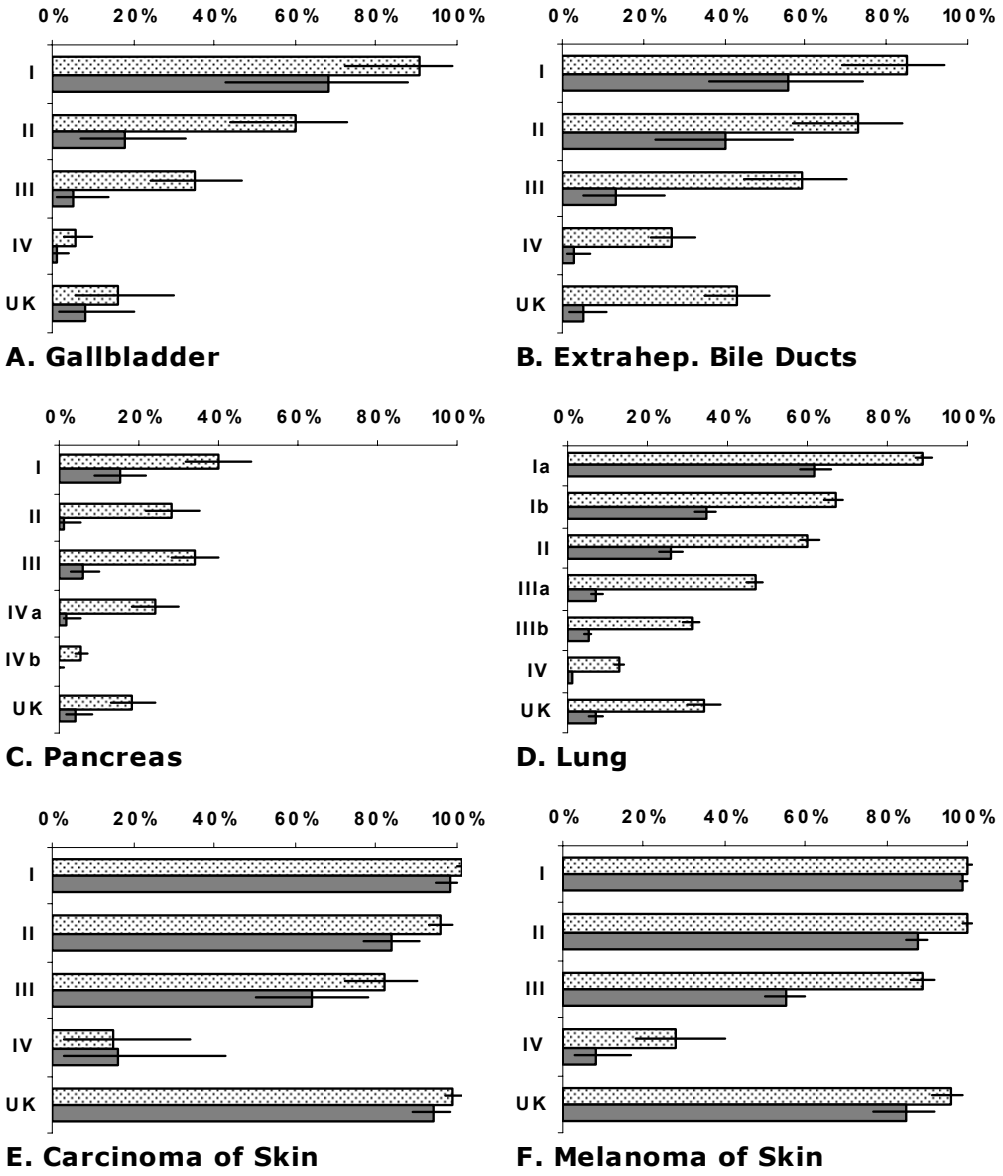

Figure 3. One-year (⊡) and five-year (■) relative survival rates of patients diagnosed with gastro-intestinal, lung or skin cancer according to TNM-stage, North-Holland/Flevoland, the Netherlands, 1989-2001 (UK=unknown). Lines represent 95% confidence intervals.

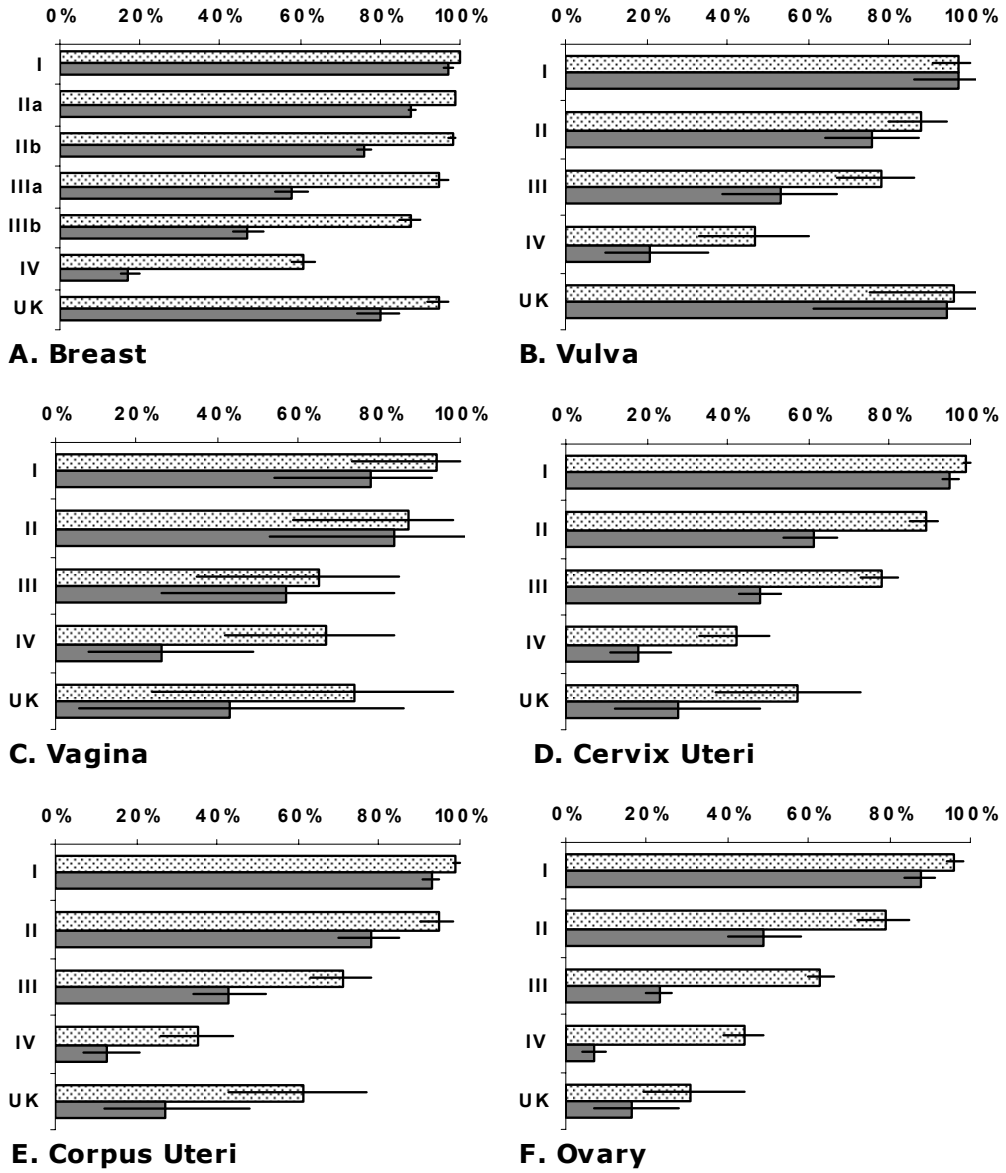

Figure 4. One-year (⊡) and five-year (■) relative survival rates of patients diagnosed with breast or gynaecological cancer according to TNM-stage, North-Holland/Flevoland, the Netherlands, 1989-2001 (UK=unknown). Lines represent 95% confidence intervals.

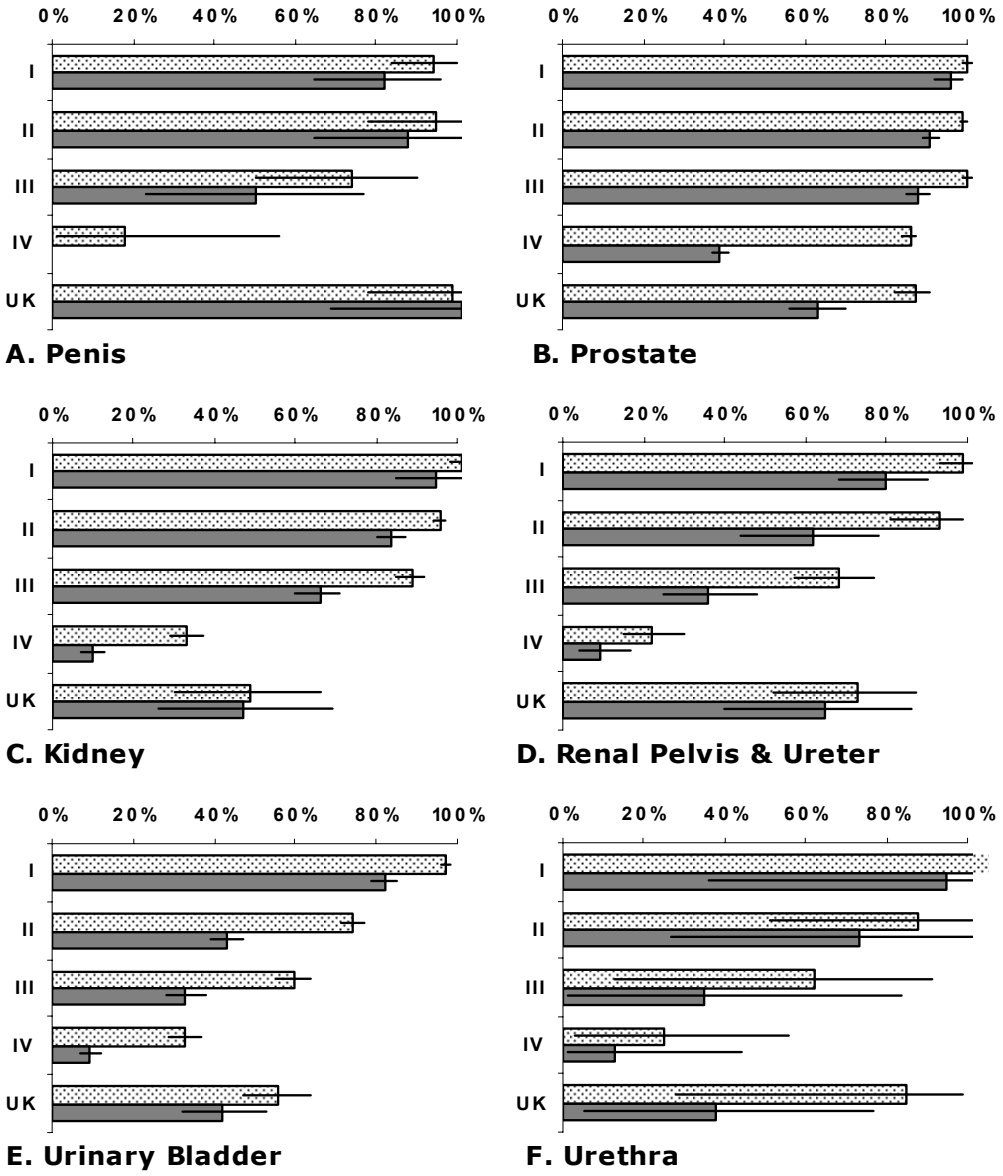

Figure 5. One-year (⊡) and five-year (■) relative survival rates of patients diagnosed with cancer of the male genitals or urinary organs according to TNM-stage, North-Holland/Flevoland, the Netherlands, 1989-2001 (UK=unknown). Lines represent 95% confidence intervals.

No gender differences in stage-specific survival of lung or colorectal carcinoma were observed (table 2). However, stage-specific survival of melanoma was more favourable in females, while stage-specific survival of bladder carcinoma was more favourable in males. Gender differences in survival for all stages combined were also observed for carcinoma of the larynx (higher survival in males), pharynx and thyroid (higher survival in females). This was mainly due to differences in stage distribution according to gender and no significant differences in stage-specific survival were observed (results not shown).

Table 2. Percentage 5-year relative survival for selected sites according to stage and gender, North-Holland/Flevoland, the Netherlands, 1989-2001

Stage at diagnosis	*Gender*					
	males			*females*		
	cases		*% survival (95% confidence interval)*	*cases*		*% survival (95% confidence interval)*
	n	*%*		*n*	*%*	
Colon/rectum						
stage I	1 393	18%	**95** (92-98)	1 346	18%	**96** (93-99)
stage II	2 410	32%	**74** (71-76)	2 507	33%	**74** (72-77)
stage III	1 900	25%	**51** (48-54)	2 020	26%	**48** (45-51)
stage IV	1 631	22%	**4** (3-5)	1 504	20%	**4** (3-5)
unknown	241	3%	**36** (28-45)	273	4%	**36** (28-44)
all stages	7 575		**55** (54-57)	7 650		**56** (55-57)
Lung						
stage Ia	722	6%	**59** (55-64)	272	6%	**68** (61-74)
stage Ib	1 620	13%	**34** (31-37)	414	10%	**38** (33-43)
stage II	956	8%	**26** (22-29)	233	6%	**28** (22-35)
stage IIIa	1 680	14%	**8** (7-10)	585	14%	**9** (6-11)
stage IIIb	2 570	21%	**4** (4-5)	915	22%	**5** (4-7)
stage IV	3 999	33%	**1** (1-1)	1 597	38%	**1** (1-2)
unknown	561	5%	**5** (3-7)	173	4%	**13** (8-19)*
all stages	12 108		**13** (12-13)	4 189		**13** (12-14)
Melanoma						
stage I	931	48%	**98** (95-100)	1 561	56%	**100** (98-101)
stage II	574	30%	**83** (79-87)	761	27%	**91** (88-94)*
stage III	324	17%	**49** (42-56)	134	5%	**61** (54-68)
stage IV	39	2%	**11** (4-24)	26	1%	**0**
unknown	69	4%	**79** (63-92)	132	5%	**88** (78-95)
all stages	1 937		**83** (81-86)	2 781		**92** (90-93)*
Bladder						
stage I	1 644	48%	**83** (80-86)	356	37%	**78** (72-85)
stage II	855	25%	**45** (41-50)	240	25%	**37** (29-45)
stage III	402	12%	**38** (32-44)	137	14%	**20** (13-29)*
stage IV	428	12%	**8** (5-12)	185	19%	**9** (5-14)
unknown	108	3%	**47** (34-60)	42	4%	**29** (14-46)
all stages	3 437		**58** (56-60)	960		**45** (41-48)*

* survival in males differs from survival in females (P<0.05)

The 3-year RSR for all stages combined increased significantly between 1989-91 and 1999-2001 for carcinomas of the breast, colon/rectum and prostate, but not for lung carcinoma (table 3). Nevertheless, we observed an increase in the 3-year RSR for the lower stages of non-small cell lung carcinoma (NSCLC).

Table 3. Percentage 3-year relative survival according to stage and period of diagnosis, North-Holland/Flevoland, the Netherlands

Stage at diagnosis	*Period of diagnosis*					
	1989-1991			*1999-2001*		
	cases		*% survival (95% confidence interval)*	*cases*		*% survival (95% confidence interval)*
	n	*%*		*n*	*%*	
Colon/rectum						
stage I	612	19%	**96** (92-99)	624	17%	**96** (93-99)
stage II	999	31%	**76** (73-80)	1 246	33%	**81** (78-84)
stage III	798	25%	**57** (54-61)	1 018	27%	**65** (61-69)
stage IV	659	21%	**5** (4-7)	771	20%	**13** (11-16)*
unknown	105	3%	**38** (27-50)	112	3%	**36** (25-49)
all stages	3 173		**59** (57-61)	3 771		**64** (62-66)*
Lung, small cell carcinoma						
stage I and II	96	12%	**15** (9-24)	39	6%	**24** (11-40)
stage IIIa	121	15%	**12** (7-18)	105	15%	**12** (6-20)
stage IIIb	125	15%	**7** (3-13)	150	22%	**9** (5-15)
stage IV	394	49%	**1** (1-3)	382	55%	**2** (1-4)
unknown	72	9%	**8** (3-16)	18	3%	**6** (0-25)
all stages	808		**9** (4-8)	694		**6** (5-9)
Lung, non-small cell carcinoma						
stage Ia	229	8%	**66** (59-73)	195	7%	**86** (79-92)*
stage Ib	481	16%	**39** (35-44)	326	11%	**54** (48-60)*
stage II	288	10%	**29** (24-35)	214	7%	**42** (34-50)
stage IIIa	434	14%	**13** (10-17)	354	12%	**18** (13-22)
stage IIIb	602	20%	**6** (6-9)	664	23%	**9** (6-11)
stage IV	769	26%	**2** (1-3)	1 074	37%	**3** (2-4)
unknown	210	7%	**11** (7-17)	62	2%	**16** (8-28)
all stages	3 013		**19** (17-20)	2 889		**20** (19-22)
Breast						
stage I	1 166	29%	**97** (96-99)	2 023	36%	**100** (99-101)
stage IIa	1 296	32%	**91** (89-93)	1 724	31%	**97** (95-98)*
stage IIb	817	20%	**84** (81-87)	1 032	19%	**89** (87-92)
stage IIIa	157	4%	**62** (54-70)	184	3%	**69** (60-76)
stage IIIb	189	5%	**58** (50-66)	261	5%	**60** (52-67)
stage IV	268	7%	**32** (26-38)	296	5%	**28** (23-34)
unknown	128	3%	**89** (80-95)	58	1%	**76** (61-88)
all stages	4 021		**85** (83-86)	5 578		**90** (89-91)*
Prostate						
stage I	91	4%	**104** (91-114)	75	2%	**99** (86-107)
stage II	887	43%	**92** (86-95)	1 716	54%	**99** (96-101)
stage III	216	10%	**92** (79-95)	667	21%	**97** (94-101)
stage IV	670	32%	**47** (32-41)	685	22%	**60** (55-64)*
unknown	215	10%	**72** (54-72)	40	1%	**64** (40-85)
all stages	2 079		**76** (68-74)	3 183		**90** (88-92)*

* survival in 1999-2001 differs from survival in 1989-1991 (P<0.05)

The 3-year RSR for stage Ia increased from 66% to 86%, for stage Ib from 39% to 54% and for stage II from 29% to 42%. This increase in RSR for the lower stages of NSCLC coincided with a decrease in the proportion of early stages of NSCLC. The proportion of stage I decreased from 24% in 1989-91 to 18% in 1999-2001, stage II de-

creased from 10% to 7% and stage IIIa from 14% to 12%. The proportions of stages IIIb and IV increased.
The 3-year RSR increased for all stages of colorectal carcinoma, except for stage I. The largest increase was observed for stages III and IV (7% and 8%, respectively). The increase for stage II was 5%. The stage distribution of colorectal cancer hardly changed between 1989-91 and 1999-2001.
For breast carcinoma, the largest increases in 3-year RSR were observed for stages II and IIIa (5-7%). The increase was statistically significant for stage IIa only. The 3-year RSR of stage I breast carcinoma increased by 3% to reach 100% in 1999-2001, while no increase was observed for stage IV breast carcinoma.
For stage I to III prostate carcinoma the 3-year observed survival in 1999-2001 almost equalled expected survival (RSR 97-99%), but the largest increase was observed for stage IV (47% in 1989-91, 60% in 1999-2001).

4. DISCUSSION

The Amsterdam Cancer Registry is one of few population-based cancer registries worldwide collecting data on stage and follow-up. The excellent population registers in the Netherlands enabled us to obtain near complete data on the vital status of 108 000 cancer patients diagnosed in 1989-2001. Stage-specific 5-year RSRs ranged from close to 100% for stage I carcinoma of the salivary glands, thyroid, colon/rectum, skin, breast, female genital organs, prostate and urethra to 1% or less for stage IV carcinoma of the oesophagus, stomach, liver, gallbladder, pancreas and lung. Although the poor survival for metastatic disease may be somewhat disappointing, it reflects common knowledge and is an indication for a high level of completeness of follow-up in our data.
Comparison to other registries is hampered by a variety of factors. The observed RSRs were generally equal to the rates from another Dutch registry with similar methods as our registry, the Eindhoven Cancer Registry [13], but table 4 shows that our rates are generally lower than in the USA according to SEER Program data [14,15]. This difference might be real, but could also be caused by a lower level of completeness of follow-up in SEER-data, as suggested by relatively high RSRs for stage IV disease in the USA. Differences in staging procedures also might influence stage-specific RSRs. For example, in endometrial carcinoma the stage-specific RSRs are lower in our data than in SEER-data, but the difference for all stages combined is only 1%. As survival of cases with unknown stage is rather high according to SEER, these cases also comprise many cases with localised disease, while in our data the cases with unknown stage are mostly cases with advanced disease. This implies that the level of certainty of the reported TNM-stage differs considerably between our data and the SEER-data. Screening procedures may also influence stage-specific survival. Although screening for prostate specific antigen (PSA) also occurred in our region to some extent, prostate cancer incidence in the USA is twice as high [16] and the vast majority of localised prostate cancers in the USA is detected by PSA-screening. These cases have a survival which equals or even exceeds the survival of the general population, which was also observed for stage I prostate carcinoma in our region. A higher socio-economic status of patients with prostate carcinoma detected by PSA-screening might contribute to this

observation. Finally, more aggressive treatment regimens in the USA may have caused a better survival in the USA than in the Netherlands [17,18].

Table 4. Five-year relative survival rates for selected cancer sites according to stage in the Netherlands (1989-2001) and the United States of America (1990-1999)

Cancer site/ stage	*cancer registry*		*Cancer site/ stage*	*cancer registry*	
	*ACR**	*SEER***		*ACR**	*SEER***
	% survival	*% survival*		*% survival*	*% survival*
Colon and rectum			Breast		
stage I	95	95	stage I	97	100
stage II	74	82	stage II	83	85
stage III	50	57	stage III	52	58
stage IV	4	7	stage IV	17	19
unknown	36	61	unknown	80	80
all stages	56	62	all stages	82	86
Lung			Corpus uteri		
stage I	44	56	stage I	93	98
stage II	26	32	stage II	78	82
stage III	6	9	stage III	43	62
stage IV	1	2	stage IV	13	28
unknown	7	16	unknown	27	71
all stages	13	15	all stages	83	84
Prostate			Ovary		
stage I	96	100	stage I	88	94
stage II	91	100	stage II	49	78
stage III	88	100	stage III	23	45
stage IV	39	53	stage IV	7	19
unknown	63	100	unknown	16	49
all stages	76	96	all stages	37	53

* The ACR (Amsterdam Cancer Registry) covers 17% of the population of the Netherlands
** Based on 9 SEER (Surveillance, Epidemiology, and End Results) Registries which cover approximately 9.5% of the population of the United States

Gender differences in stage-specific survival were confined to melanoma and bladder carcinoma, probably caused by differences in distribution according to subsite (melanoma) and anatomical dissimilarities (bladder).
Although the overall survival of patients with lung cancer was poor and no significant increase in overall survival was observed over time, the increase in survival of the lower stages of NSCLC was remarkable. As this increase in survival coincided with a decrease in the proportion of lower and unknown stages, while the proportion of the higher stages increased, this phenomenon (stage migration) is probably caused by improved staging procedures for lung cancer, as described earlier by Feinstein and colleagues [19]. In 1999, imaging with positron emission tomography (PET) was introduced in our region for preoperative staging of NSCLC patients. Consequently, the total number of thoracotomies and the number of futile thoracotomies decreased [20], while the patients without lymph node metastasis who remained eligible for a thoracotomy, experienced an improved survival.
Stage-specific survival of breast cancer patients increased for stages I-IIIb. Although the stage distribution of patients with breast cancer changed between 1989-91 and 1999-2001, improved staging procedures are less likely to have caused the improved

survival. Axillary lymph node dissections were routinely performed throughout the study period and no stage migration towards higher stages was observed. To the contrary, the proportion of lower stages increased between 1989-91 and 1999-2001, due to the start of the breast cancer screening in 1990. Because the overall incidence of breast cancer increased by 25% between 1990 and 2000 and even by 40% for women between 50 and 70 years of age [21], overdiagnosis of screen-detected breast cancers may have occurred. This phenomenon may have contributed to improved survival in early stage breast cancer. It is likely that adjuvant treatment of breast cancer with hormones and/or chemotherapy also has contributed to improved survival [22], as its application gradually increased between 1989-91 and 1999-2001 in our region, from 11% to 24% in stage I, from 35% to 75% in stage IIa and from 70% to 90% in stage IIb. In a study of Vervoort and colleagues, the increased adjuvant treatment in the Netherlands is predicted to reduce breast cancer mortality in women aged 55-74 years by 7% in the year 2007 [23]. Finally, stage migration within stages may have contributed to improved survival. For example, in stage I the proportion of tumours with a diameter of 1 cm or less (T1a/b) increased from 23% in 1989-91 to 32% in 1999-2001 and in stage IIa the proportion of tumours with a diameter of 2 cm or less (T1) increased from 38% in 1989-91 to 55% in 1999-2001.

Overdiagnosis of previously unnoticed cases may have contributed to improved survival of localised prostate cancer. Between 1989-91 and 1999-2001, the number of localised carcinomas doubled (mostly due to PSA screening), while the number of stage IV carcinomas hardly increased. However, the increase in the RSR for stage IV prostate carcinoma cannot be attributed to effects of early detection and a more likely explanation relates to changes in the hormonal treatment of stage IV carcinoma. In localised prostate carcinoma, treatment may also have improved survival, as the percentage of patients with wait-and-see policy decreased in favour of the percentage of patients who underwent a prostatectomy or curative radiotherapy.

The stage distribution of colorectal cancer hardly changed in the 1990s. So, the increase in survival of colorectal cancer cannot be attributed to improved staging procedures or early detection. Most likely, changes in treatment practices have contributed to an improved stage-specific survival of colorectal cancer. Between 1989-91 and 1999-2001, the proportion of patients with stage III colon carcinoma who received adjuvant chemotherapy increased from 5% to 49% and the application of radiotherapy for stage II/III rectal carcinoma changed from post-operative to pre-operative. Also, the surgical procedures for rectal surgery improved by the introduction of the total mesorectal excision in 1996/97. As the survival of colorectal carcinoma mainly increased in stages II and III, and the largest increase was observed for rectal carcinoma (results not shown), the above changes in the treatment of colorectal cancer are likely to have caused the improvement in survival [24]. In stage IV colorectal carcinoma, the increased application of metastasectomy (in 3% and 6% of patients in 1989-91 and 1999-2001, respectively) and increased treatment with chemotherapy (15% and 42% in 1989-91 and 1999-2001, respectively) may have contributed to an increased survival.

In conclusion, in comparison to 1989-91 improved stage-specific RSRs were observed for the most common cancers diagnosed in 1999-2001, probably related to screening (breast, prostate), treatment (breast, colon/rectum, prostate) and staging procedures

(lung). Improved stage-specific RSRs may contribute to an overall improvement of the survival of specific cancers and, in the end, a decreased mortality due to these cancers, but, as the results for lung cancer show, this is not necessarily so.

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APPENDIX 1

One-, five- and ten-year relative survival of patients in North-Holland/Flevoland, the Netherlands, in 1989-2001, according to site and TNM-stage

Site and stage	*Number of cases*	*1-year relative survival (95% CI)*	*5-year relative survival (95% CI)*	*10-year relative survival (95% CI)*
Lip and Oral Cavity				
I	655	100% (98% - 101%)	91% (87% - 95%)	80% (73% - 88%)
II	271	95% (91% - 98%)	80% (72% - 87%)	63% (51% - 74%)
III	171	75% (67% - 81%)	49% (40% - 58%)	31% (21% - 42%)
IV	483	65% (60% - 69%)	36% (31% - 41%)	25% (20% - 32%)
unknown	57	91% (79% - 97%)	81% (64% - 94%)	71% (47% - 93%)
Pharynx				
I	45	94% (81% - 100%)	69% (50% - 84%)	45% (24% - 66%)
II	86	91% (82% - 96%)	70% (57% - 81%)	46% (29% - 64%)
III	185	81% (74% - 86%)	61% (52% - 69%)	46% (35% - 56%)
IV	559	71% (67% - 75%)	31% (27% - 35%)	24% (19% - 30%)
unknown	8	51% (15% - 79%)	39% (9% - 70%)	20% (1% - 58%)
Larynx				
I	527	100% (98% - 101%)	92% (87% - 96%)	83% (74% - 91%)
II	338	94% (90% - 97%)	71% (64% - 77%)	56% (48% - 65%)
III	153	86% (79% - 91%)	58% (48% - 67%)	35% (24% - 47%)
IV	312	72% (66% - 77%)	44% (38% - 50%)	36% (28% - 45%)
unknown	11	68% (32% - 90%)	41% (10% - 77%)	28% (3% - 72%)
Maxillary Sinus				
I/II	6	74% (22% - 100%)	54% (3% - 122%)	54% (2% - 122%)
III	17	98% (68% - 103%)	37% (13% - 64%)	40% (15% - 70%)
IV	38	60% (42% - 74%)	24% (11% - 40%)	28% (13% - 47%)
unknown				
Salivary Glands				
I	88	101% (94% - 102%)	97% (87% - 103%)	104% (89% - 113%)
II	26	96% (76% - 102%)	68% (42% - 88%)	55% (28% - 79%)
III	14	99% (63% - 105%)	43% (14% - 76%)	47% (15% - 83%)
IV	52	68% (53% - 80%)	27% (14% - 43%)	9% (1% - 30%)
unknown	25	79% (56% - 92%)	63% (37% - 84%)	54% (22% - 88%)
Thyroid Gland				
I	285	99% (97% - 100%)	99% (96% - 100%)	99% (95% - 101%)
II	125	99% (94% - 101%)	98% (90% - 103%)	95% (81% - 105%)
III	125	87% (79% - 92%)	77% (66% - 86%)	68% (53% - 82%)
IV	114	37% (28% - 46%)	12% (6% - 20%)	9% (3% - 19%)
unknown	15	69% (38% - 88%)	64% (30% - 91%)	54% (15% - 100%)
Oesophagus				
I	72	95% (85% - 100%)	82% (67% - 93%)	86% (67% - 102%)
IIa	155	75% (67% - 82%)	32% (24% - 41%)	18% (9% - 29%)
IIb	84	63% (52% - 73%)	26% (16% - 37%)	21% (10% - 35%)
III	385	37% (32% - 42%)	8% (5% - 11%)	7% (4% - 11%)
IV	559	16% (13% - 19%)	1% (0% - 3%)	
unknown	728	33% (29% - 37%)	5% (3% - 7%)	5% (3% - 8%)

One-, five- and ten-year relative survival of patients in North-Holland/Flevoland, the Netherlands, in 1989-2001, according to site and TNM-stage (continued)

Site and stage	*Number of cases*	*1-year relative survival (95% CI)*	*5-year relative survival (95% CI)*	*10-year relative survival (95% CI)*
Stomach				
Ia	253	85% (79% - 89%)	82% (74% - 89%)	76% (63% - 87%)
Ib	431	85% (81% - 89%)	60% (53% - 66%)	50% (41% - 60%)
II	499	72% (68% - 76%)	33% (28% - 38%)	28% (23% - 35%)
IIIa	538	53% (49% - 57%)	15% (12% - 19%)	10% (7% - 15%)
IIIb	138	56% (47% - 64%)	10% (6% - 17%)	5% (2% - 14%)
IV	1695	13% (11% - 15%)	1% (1% - 2%)	
unknown	733	24% (21% - 27%)	5% (3% - 7%)	3% (1% - 7%)
Small Intestines				
I	14	74% (42% - 91%)	65% (31% - 90%)	60% (26% - 89%)
II	49	68% (52% - 80%)	38% (22% - 55%)	45% (26% - 65%)
III	37	69% (51% - 82%)	29% (14% - 47%)	29% (12% - 50%)
IV	51	26% (15% - 39%)	7% (2% - 18%)	4% (0% - 17%)
unknown	13	16% (2% - 41%)		
Colon and Rectum				
I	2739	97% (96% - 98%)	95% (93% - 97%)	91% (87% - 95%)
II	4917	89% (88% - 90%)	74% (72% - 76%)	70% (67% - 73%)
III	3920	85% (84% - 86%)	50% (48% - 52%)	44% (42% - 47%)
IV	3135	33% (31% - 35%)	4% (3% - 5%)	3% (2% - 4%)
unknown	514	58% (53% - 63%)	36% (30% - 42%)	30% (23% - 38%)
Anus				
I	30	99% (80% - 102%)	83% (59% - 97%)	87% (58% - 106%)
II	95	88% (79% - 94%)	68% (54% - 80%)	64% (45% - 81%)
III	60	89% (77% - 96%)	39% (25% - 53%)	25% (10% - 44%)
IV	11	28% (6% - 56%)		
unknown	33	87% (68% - 97%)	59% (34% - 82%)	37% (11% - 74%)
Liver				
I/II	72	48% (36% - 60%)	22% (12% - 35%)	16% (5% - 33%)
III	84	41% (30% - 52%)	13% (5% - 24%)	9% (2% - 22%)
IV	228	14% (10% - 19%)	1% (0% - 4%)	1% (0% - 4%)
unknown	92	12% (6% - 20%)	2% (1% - 8%)	
Gallbladder				
I	31	91% (72% - 99%)	68% (43% - 88%)	61% (30% - 92%)
II	49	60% (44% - 73%)	18% (7% - 33%)	16% (5% - 37%)
III	68	35% (24% - 47%)	5% (1% - 14%)	6% (1% - 24%)
IV	212	6% (3% - 10%)	1% (0% - 4%)	1% (0% - 4%)
unknown	39	16% (6% - 30%)	8% (2% - 20%)	9% (2% - 21%)
Extrahepatic Bile Ducts				
I	40	85% (69% - 94%)	56% (36% - 74%)	49% (25% - 74%)
II	45	73% (57% - 84%)	40% (23% - 57%)	46% (27% - 66%)
III	60	59% (45% - 70%)	13% (5% - 25%)	4% (0% - 16%)
IV	242	27% (22% - 33%)	3% (1% - 7%)	3% (1% - 7%)
unknown	147	43% (35% - 51%)	5% (2% - 11%)	5% (1% - 12%)
Pancreas				
I	163	40% (32% - 48%)	15% (9% - 22%)	10% (4% - 22%)
II	176	28% (22% - 35%)	1% (0% - 5%)	1% (0% - 4%)
III	215	34% (28% - 40%)	6% (3% - 10%)	6% (3% - 11%)
IVa	210	24% (18% - 30%)	2% (1% - 5%)	
IVb	1161	5% (4% - 7%)	0% (0% - 1%)	
unknown	171	18% (13% - 24%)	4% (2% - 8%)	5% (2% - 11%)

One-, five- and ten-year relative survival of patients in North-Holland/Flevoland, the Netherlands, in 1989-2001, according to site and TNM-stage (continued)

Site and stage	Number of cases	1-year relative survival (95% CI)	5-year relative survival (95% CI)	10-year relative survival (95% CI)
Lung				
Ia	994	89% (87% - 91%)	62% (58% - 66%)	43% (37% - 48%)
Ib	2034	67% (64% - 69%)	35% (32% - 37%)	27% (24% - 31%)
II	1189	60% (58% - 63%)	26% (23% - 29%)	17% (13% - 20%)
IIIa	2265	47% (45% - 49%)	7% (6% - 9%)	4% (3% - 6%)
IIIb	3485	31% (29% - 33%)	5% (4% - 6%)	3% (2% - 3%)
IV	5596	13% (12% - 14%)	1% (1% - 1%)	1% (0% - 1%)
unknown	734	34% (30% - 38%)	7% (5% - 9%)	4% (2% - 6%)
Carcinoma of Skin				
I	3144	101% (100% - 102%)	98% (95% - 100%)	98% (93% - 103%)
II	538	96% (93% - 99%)	84% (77% - 91%)	90% (77% - 104%)
III	105	82% (72% - 90%)	64% (50% - 78%)	53% (33% - 74%)
IV	21	15% (3% - 34%)	16% (3% - 43%)	
unknown	1022	99% (97% - 101%)	94% (89% - 98%)	95% (87% - 104%)
Melanoma of Skin				
I	2492	100% (100% - 101%)	99% (98% - 100%)	99% (97% - 101%)
II	1335	100% (99% - 101%)	88% (85% - 90%)	81% (77% - 85%)
III	625	89% (86% - 92%)	55% (50% - 60%)	43% (36% - 50%)
IV	65	28% (18% - 40%)	8% (3% - 17%)	8% (3% - 17%)
unknown	201	96% (91% - 99%)	85% (77% - 92%)	77% (66% - 86%)
Breast				
I	7111	100% (100% - 100%)	97% (96% - 98%)	91% (89% - 93%)
IIa	6518	99% (99% - 99%)	88% (87% - 89%)	78% (75% - 80%)
IIb	3969	98% (97% - 99%)	76% (74% - 78%)	59% (56% - 61%)
IIIa	760	95% (93% - 97%)	58% (54% - 62%)	40% (35% - 45%)
IIIb	913	88% (85% - 90%)	47% (43% - 51%)	28% (23% - 33%)
IV	1216	61% (58% - 64%)	17% (15% - 20%)	5% (3% - 7%)
unknown	365	95% (92% - 97%)	80% (74% - 85%)	74% (67% - 82%)
Vulva				
I	132	97% (91% - 100%)	97% (86% - 105%)	87% (67% - 105%)
II	135	88% (80% - 94%)	76% (64% - 87%)	88% (68% - 106%)
III	87	78% (67% - 86%)	53% (39% - 67%)	59% (39% - 79%)
IV	54	47% (33% - 60%)	21% (10% - 35%)	8% (1% - 24%)
unknown	27	96% (75% - 104%)	94% (61% - 118%)	90% (45% - 129%)
Vagina				
I	25	94% (73% - 100%)	78% (54% - 93%)	81% (53% - 99%)
II	18	87% (59% - 98%)	84% (53% - 102%)	73% (24% - 109%)
III	16	65% (35% - 85%)	57% (26% - 84%)	65% (29% - 95%)
IV	20	67% (42% - 84%)	26% (8% - 49%)	28% (9% - 53%)
unknown	7	74% (24% - 98%)	43% (6% - 86%)	51% (7% - 102%)
Cervix Uteri				
I	938	99% (98% - 100%)	95% (93% - 97%)	91% (88% - 94%)
II	312	89% (85% - 92%)	61% (54% - 67%)	53% (45% - 62%)
III	407	78% (73% - 82%)	48% (43% - 53%)	39% (33% - 46%)
IV	134	42% (33% - 50%)	18% (11% - 26%)	19% (12% - 28%)
unknown	32	57% (37% - 73%)	28% (12% - 48%)	28% (10% - 53%)

One-, five- and ten-year relative survival of patients in North-Holland/Flevoland, the Netherlands, in 1989-2001, according to site and TNM-stage (continued)

Site and stage	*Number of cases*	*1-year relative survival (95% CI)*	*5-year relative survival (95% CI)*	*10-year relative survival (95% CI)*
Corpus Uteri				
I	1864	99% (98% - 100%)	93% (91% - 95%)	94% (90% - 98%)
II	223	95% (90% - 98%)	78% (70% - 85%)	70% (57% - 82%)
III	175	71% (63% - 78%)	43% (34% - 52%)	41% (31% - 51%)
IV	111	35% (26% - 44%)	13% (7% - 21%)	11% (5% - 19%)
unknown	41	61% (43% - 77%)	27% (12% - 48%)	34% (14% - 63%)
Ovary				
I	489	96% (94% - 98%)	88% (84% - 91%)	80% (74% - 85%)
II	164	79% (72% - 85%)	49% (40% - 58%)	35% (26% - 46%)
III	1067	63% (60% - 66%)	23% (20% - 26%)	15% (12% - 18%)
IV	422	44% (39% - 49%)	7% (4% - 10%)	4% (2% - 7%)
unknown	58	31% (19% - 44%)	16% (7% - 28%)	14% (5% - 27%)
Penis				
I	84	94% (84% - 100%)	82% (65% - 96%)	76% (51% - 100%)
II	37	95% (78% - 102%)	88% (65% - 105%)	95% (65% - 119%)
III	23	74% (50% - 90%)	50% (23% - 77%)	31% (6% - 71%)
IV	6	18% (1% - 56%)		
unknown	26	99% (78% - 105%)	101% (69% - 121%)	89% (40% - 134%)
Prostate				
I	1820	100% (99% - 101%)	96% (92% - 99%)	105% (90% - 119%)
II	4550	99% (98% - 100%)	91% (89% - 93%)	76% (72% - 81%)
III	1868	100% (99% - 101%)	88% (85% - 91%)	69% (62% - 76%)
IV	3185	86% (84% - 87%)	39% (37% - 41%)	24% (21% - 27%)
unknown	427	87% (82% - 91%)	63% (56% - 70%)	54% (44% - 66%)
Kidney				
I	234	101% (98% - 102%)	95% (85% - 102%)	75% (52% - 95%)
II	856	96% (94% - 97%)	84% (80% - 87%)	70% (64% - 75%)
III	483	89% (85% - 92%)	66% (60% - 71%)	56% (48% - 64%)
IV	599	33% (29% - 37%)	10% (7% - 13%)	7% (5% - 10%)
unknown	33	49% (30% - 66%)	47% (26% - 69%)	54% (23% - 93%)
Renal Pelvis and Ureter				
I	123	99% (93% - 101%)	80% (68% - 90%)	60% (44% - 77%)
II	55	93% (81% - 99%)	62% (44% - 78%)	37% (18% - 60%)
III	100	68% (57% - 77%)	36% (25% - 48%)	35% (22% - 49%)
IV	111	22% (15% - 30%)	9% (4% - 17%)	7% (2% - 17%)
unknown	29	73% (52% - 87%)	65% (40% - 86%)	32% (7% - 71%)
Bladder				
I	2000	97% (96% - 98%)	82% (79% - 85%)	72% (67% - 77%)
II	1095	74% (71% - 77%)	43% (39% - 47%)	35% (30% - 40%)
III	539	60% (55% - 64%)	33% (28% - 38%)	26% (19% - 33%)
IV	613	33% (29% - 37%)	9% (7% - 12%)	6% (4% - 9%)
unknown	150	56% (47% - 64%)	42% (32% - 53%)	35% (22% - 50%)
Urethra				
I	9	105%	95% (36% - 120%)	43% (5% - 99%)
II	12	88% (51% - 101%)	73% (27% - 107%)	
III	5	62% (13% - 91%)	35% (1% - 84%)	
IV	8	25% (3% - 56%)	13% (1% - 44%)	
unknown	6	85% (28% - 99%)	38% (5% - 77%)	49% (7% - 99%)

4.2 Epidemiology and survival in patients with carcinoid disease in the Netherlands. An epidemiological study with 2391 patients.

Quaedvlieg PF, Visser O, Lamers CB, Janssen-Heijen ML, Taal BG. Epidemiology and survival in patients with carcinoid disease in The Netherlands. An epidemiological study with 2391 patients.
Ann Oncol. 2001 Sep;12(9):1295-300.

ABSTRACT

Background
Carcinoid tumours are rare malignant neuro-endocrine tumours. In 1992 octreotide was introduced in The Netherlands as a palliative treatment for the carcinoid syndrome in metastatic carcinoid disease. The aims of this epidemiological study were to evaluate epidemiological data and the impact of octreotide on survival in metastatic carcinoid disease.
Methods
Between 1989 and 1996, 2391 patients with carcinoid disease were diagnosed in the Netherlands. Survival data from two Registries were available in 619 patients, diagnosed between 1980 and 1997.
Results
Between 1989-1996, incidence was 1.95/100 000 population. Under the age of 50 years a significant female predominance was observed. Under the age of 35 years, appendiceal carcinoid was the most frequently diagnosed primary site. Incidence of distant metastases at diagnosis for appendix and lung primary sites was 1.6% and 5.5%, compared to 40% in the other primary sites. Multivariate analysis of 619 patients revealed that age, stage and appendix localization independently predicted survival, however, only year of diagnosis after 1992 independent predicted survival (p=0.012).
Conclusions
The female predominance found under the age of 50 years suggests hormonal influence. Improved survival in metastatic carcinoid disease might relate to the use of octreotide.

INTRODUCTION

In 1907 Oberndorfer[1] investigated tumours originating in the ileum of six patients who died from other causes in a necropsy study. He proposed the name "Karzinoid" (carcinoma-like), as he did not find any infiltration in surrounding tissues or distant metastases in these specimens. However, in 1890 Ransom[2] described a patient with a carcinoid syndrome and liver metastases: pain after food intake followed by diarrhoea, attacks of dyspnoea, a grossly enlarged liver with numerous cancerous nodules and a polypoid growth in the ileum of the size of a walnut.
As carcinoid tumours arise from cells of the diffuse neuro-endocrine system, almost any site can be affected. However, most carcinoid tumours originate from the gastrointestinal tract or the lungs. Peptide production is the hallmark of the disease[3], resulting in substantial morbidity (i.e. flushing, diarrhoea and/or wheezing, known as the carcinoid syndrome) in approximately 10% of the patients (mostly with liver metastases). The most frequently detected peptide responsible for the carcinoid syndrome is serotonin, described by Lembeck[4] in 1953. Serotonin is synthesized by the decarboxylation of 5-hydroxytryptophan, a derivative of tryptophan. Serotonin is subsequently metabolized by monoamine oxidase to 5-hydroxy indole acetic acid (5-HIAA) and excreted in the urine.
Carcinoid tumours are rare and the incidence is approximately 5% of the incidence of cancer of the colon[5]. Carcinoid tumours are malignant, but even in the presence of metastatic disease these tumours often have an indolent nature. When metastatic disease is present, treatment is primarily aimed at palliation of the incapacitating symptoms of the carcinoid syndrome with somatostatin analogues, interferon-α or MIBG[6]. Surgery is indicated for the primary tumour in case of obstruction. However, in metastatic disease of the liver palliative resection is usually not feasible due to involvement of both liver lobes.
The aim of this study was to evaluate epidemiological data of carcinoid tumours in the Netherlands and to investigate whether survival has improved since 1992, when octreotide became available nationwide.

PATIENTS AND METHODS

The Netherlands Cancer Registry (NCR), which has been operating since 1989, is a population-based cancer registry, with systematic collection of data on all malignant neoplasms. The NCR consists of nine regional registries, each part of a comprehensive cancer centre. In all Dutch hospitals, pathologists enter their coded histological diagnoses in a computer system, which notifies one of the regional cancer centres [5]. The cancer registries do not register patients treated by a general practitioner only. This well known systematic under-registration for all cancers is estimated to be 1.3% for the registry of the Comprehensive Cancer Centre Zuid-Nederland and at 1.6% in the registry of the Comprehensive Cancer Centre Limburg[7,8]. Due to occasional errors and shortcomings in notification procedures, additional incompleteness is possible.
The database of the NCR was searched for patients with carcinoid tumours, i.e. all ICD-O M-8240/* codes (thus excluding argentafinomas, Goblet cell carcinoids, APUDomas and patients with mixed tumours), diagnosed from 1989 until 1996. To compare incidence rates between different populations, age-adjusted incidence rates were

calculated. For the calculation of the European standardised rates (ESR), the European Standard Population was used [9]. For estimation of survival, only data from two regions (Comprehensive Cancer Centre South 1980-1992 and Comprehensive Cancer Centre Amsterdam 1988-1997) were available. Unfortunately cause of death was not available. Survival was calculated as crude and as relative survival, using a computer program from the Finnish cancer registry [10]. Statistical analysis, including the Kaplan-Meier estimates of survival and the Cox multivariate regression analysis were performed using Stata 6.0 for Windows. To detect survival differences that could relate to the use of somatostatin analogues since 1992, patients with metastatic disease from primary midgut, lung and unknown primary site were selected for their probability of displaying the carcinoid syndrome, excluding patients with primary rectal and GIT foregut tumours. For this purpose only, patients that died within 3 months after diagnosis were excluded from this analysis, as they probably did not receive (long-term) octreotide therapy.

RESULTS

Incidence data

The total number of patients registered from 1989 until 1997 was 2391. The annual total number of new patients with carcinoid disease ranged from 218 to 331. Discarding the first year of registration, European Standardised Incidence Rates remained stable at 1.95/100 000, evenly distributed between both sexes (Table 1).

Table 1. Incidence of carcinoid tumours in the Netherlands, 1989-1996

	Men		Women		Women	
	n	ESR	n	ESR	n	ESR
1989	95	1.4	124	1.5	219	1.4
1990	134	1.9	170	2.0	304	2.0
1991	138	2.0	153	1.8	291	1.9
1992	145	2.0	172	2.1	317	2.0
1993	136	1.9	168	2.0	304	1.9
1994	136	1.8	169	1.9	305	1.9
1995	167	2.2	175	2.0	342	2.1
1996	133	1.8	176	2.0	309	1.9

Source: Netherlands Cancer Registry
ESR = European Standardised Rate

Two peaks could be identified in the age-specific incidence rates: a small one (±1.5/100000) between 15 and 25 years, consisting of considerably more women than men, and a large one (± 7.5-9.5/100 000) between 65-75 years, with a male predominance. Under the age of 50 a female predominance could be observed, both for the appendix and the bronchopulmonary primary sites (Figure 1).

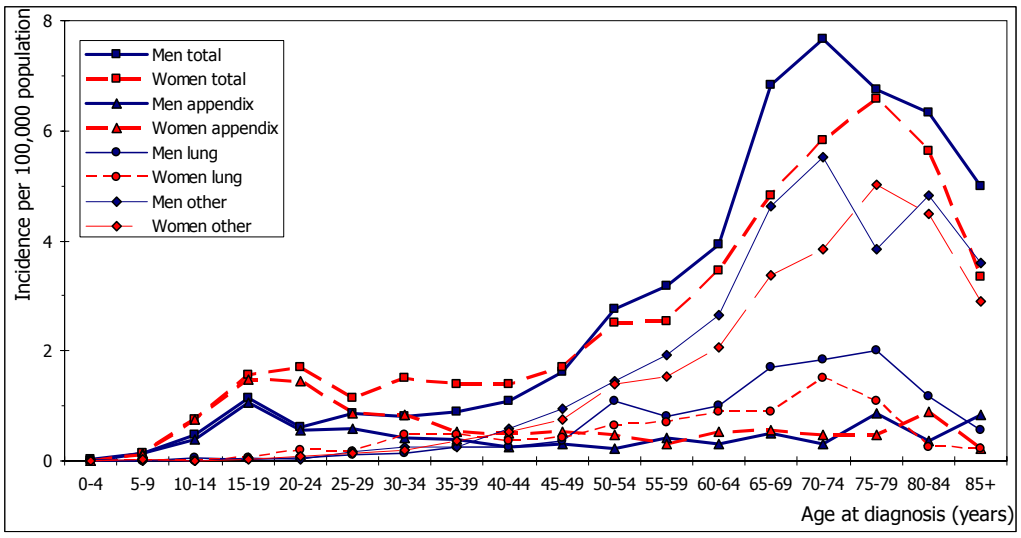

Figure 1. Age-specific incidence of carcinoid disease in the Netherlands according to gender and localisation of the primary tumour, 1989-1996 (n=2391).
Source: Netherlands Cancer Registry

Table 2. Carcinoid tumours in the Netherlands according to primary site and age group, 1989-1996

	Age group (years)					*Total*
	< 30	*30-44*	*45-59*	*60-74*	*> 74*	
Head and neck						
Larynx	-	-	3	5	2	10
Middle ear	2	2	5	-	-	9
Other	-	1	-	3	-	4
Gastro-intestinal						
Stomach	2	2	26	48	26	104
Small bowel	7	24	67	155	96	349
Appendix	318	153	82	64	37	654
Large bowel (excl. appendix)	3	10	26	52	44	135
Rectum	3	28	44	42	19	136
Pancreas	1	8	18	32	9	68
Liver	-	2	1	3	3	9
Other	1	3	10	19	4	37
Lung-mediastinum						
Lung	32	93	142	190	68	525
Thymus/mediastinum	2	3	5	6	1	17
Breasts	-	2	1	4	10	17
Urogenital						
Ovaries	1	4	3	7	2	17
Prostate	-	-	-	1	3	4
Other	2	1	-	2	1	6
Other sites	-	-	-	-	1	1
Unknown primary site	1	19	66	136	67	289
Total	375	355	499	769	393	2 391

Source: Netherlands Cancer Registry

The main primary sites were: appendix (27%) and lung (22%). In 12% the site of the primary tumour was unknown. Of all 2391 carcinoid tumours, 1492 (62%) were located in the gastro-intestinal tract. In only 68 cases (3%) a primary site outside the gastro-intestinal tract or the bronchopulmonary tree was identified. Appendiceal carcinoid was more frequent in young people: 72% was younger than 45 years (Table 2).
Presentation with distant metastases was found in 22%; in 11% stage of disease was unknown. The distribution of patients with an unknown stage between the various subgroups was similar. In lung or appendiceal primary site presentation with distant metastases was seen in only 4.8% and 1.5%. Among all patients with distant metastases a primary site was identified in only 45% (Table 3).

Table 3. Carcinoid tumours in the Netherlands according to stage, 1989-1996

	Distant metastases	*Loco-regional disease*	*Unknown stage*	*All*
Head and neck				
Larynx	1	8	1	10
Middle ear	-	5	4	9
Other	-	4	-	4
Gastro-intestinal				
Stomach	9	69	26	104
Small bowel	90	197	62	349
Appendix	10	575	69	654
Large bowel (excl. appendix)	44	81	10	135
Rectum	10	118	8	136
Pancreas	29	28	11	68
Liver	-	6	3	9
Other	10	17	10	37
Lung-mediastinum				
Lung	25	456	44	525
Thymus/mediastinum	1	11	5	17
Breasts	2	15	-	17
Urogenital				
Ovaries	3	12	2	17
Prostate	1	3	-	4
Other	-	6	-	6
Other sites	-	1	-	1
Unknown primary site	289			289
Total	524	1612	255	2 391

Source: Netherlands Cancer Registry

Survival data

Stage of disease influenced prognosis significantly: overall relative five-year survival rates for local disease was 93%, for regional disease 74% and for distant metastases 19%, differences between stages were statistically significant ($p<0.05$, using the log-rank test). For localised disease relative 5-year survival rates were not significantly different between the different primary sites, (table 4).
Using the Cox multivariate regression analysis for 619 cases and six co-variates (age, gender, stage of disease, primary localisation [appendix, lung, midgut, unknown], period of diagnosis [before or after 1992] and cancer centre [Comprehensive Cancer Centre South 1980-1992 and Comprehensive Cancer Centre Amsterdam 1988-1997]),

age (p=0.000), stage (p=0.000), gender (p=0.001) and a primary appendix localization (p=0.012) were independent predictors of survival.

Table 4. Relative survival of carcinoid tumours according to stage and primary site, Amsterdam Cancer Registry (1988-1997) and Eindhoven Cancer Registry (1980-1992)

Stage	Primary site	Cases	Five-year survival (%)	95% CI
All	All	694	72	68-77
	Appendix	198	95	91-99
	GIT, appendix excl.	227	61	53-70
	Lung	159	80	71-88
	Other	29	67	43-91
	Unknown	81	19	6-32
Localised	All	387	93	89-97
	Appendix	186	96	92-100
	GIT, appendix excl.	71	88	76-100
	Lung	116	92	84-100
	Other	14	85	53-100
Regional	All	63	74	60-88
	Appendix	8	100	100
	GIT, appendix excl.	33	85	66-100
	Lung	17	45	17-73
	Other	5	65	15-100
Distant	All	164	19	11-28
	Appendix	2	0	0
	GIT, appendix excl.	67	21	8-33
	Lung	10	0	0
	Other	4	43	0-100
	Unknown	81	19	6-33
Unknown	All	80	63	50-77
	Appendix	2	55	0-100
	GIT, appendix excl.	56	61	44-78
	Lung	16	77	50-100
	Other	6	56	13-98

Source: Amsterdam Cancer Registry, Eindhoven Cancer Registry
GIT=gastro-intestinal tract
CI=confidence interval

In patients with distant metastases from lung, midgut or unknown primary (n=107), crude survival was clearly affected by period of diagnosis (log-rank test: p=0.007, figure 2). Median survival increased from 24 to 43 months. Three-year survival increased significantly from 29% to 66%. In the Cox multivariate analysis, assembled from 5 parameters (age in 5y cohorts, gender, primary site [appendix, lung, unknown], year of diagnosis [before 1992, from 1992] and cancer centre), only period of diagnosis was an independent predictor of survival (p=0.012).

DISCUSSION

In The Netherlands, between 1990 and 1996 European Standardised incidence Rates (ESR) for carcinoid tumours remained stable at 1.95/100 000, with an equal distribution between the sexes. Six other reports concerning incidence revealed incidence

rates between 0.79 (per 100 000 in England) and 1.88 (per 100 000 in African Americans), with a slight female predominance[11,12,13,14,15,16]. An explanation for this difference could be that in The Netherlands all carcinoids, including benign appendiceal carcinoids, were entered in the database of the NCR, resulting in higher incidence rates compared to the SEER database (0.54 vs. 0.10 per 100 000). As all appendiceal carcinoids were entered in the database of the NCR, only 1.5% metastatic disease was found in patients with appendiceal carcinoid at diagnosis, compared to 8.5% found in the SEER database. In a large (n=16 294) autopsy study from in Sweden between 1958 and 1969, representing 63% of the people who died in that area, a total of 201 carcinoid tumours were found, resulting in an incidence of 8.4/100 000 population[17].

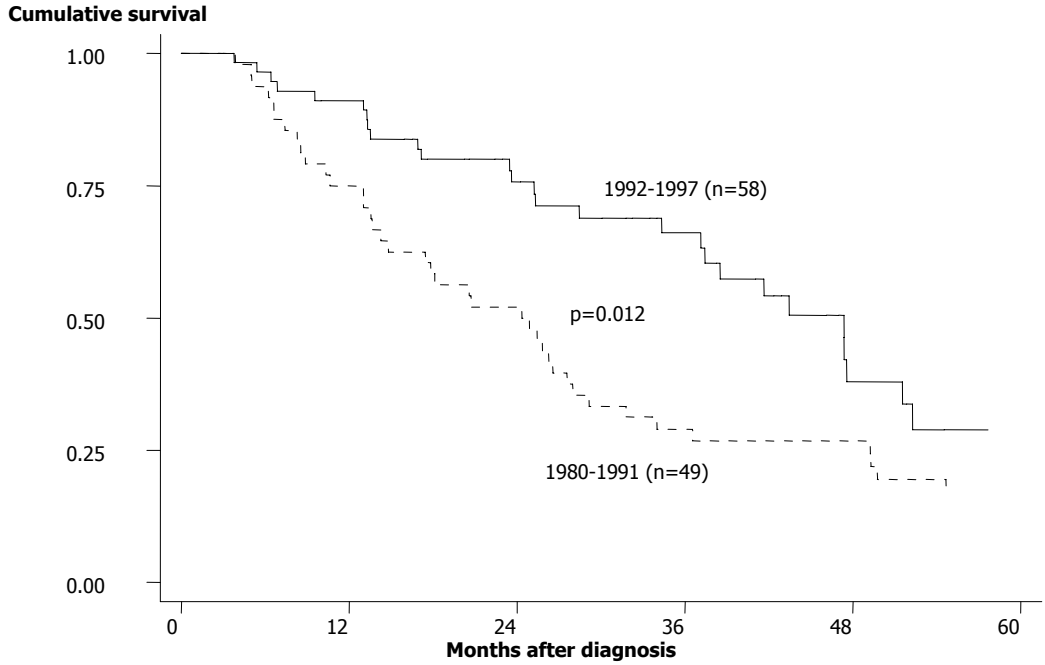

Figure 2. Overall survival in 107 carcinoid patients with distant metastases from a midgut, lung or unknown primary site, according to year of diagnosis. Univariate analysis was performed using log-rank test.
Source: Amsterdam Cancer Registry (1988-1997) and Eindhoven Cancer Registry (1980-1992).

In the present study stage of disease was unknown in 11%. This was mainly due to insufficient information in the medical records on T- and N-stage of the TNM-classification. Moreover, many carcinoid tumours were found at sites where the TNM-classification is not applicable. Although in many of those cases the extent of disease was registered, information on the extent of disease was not always available.
The overall incidence was equally distributed between the sexes. However, for the two most frequent primary sites (appendix and lung), in patients under the age of 50 years, women were affected twice as often as men (for the other primary sites differences did not reach statistical significance). For appendiceal carcinoid this might be explained by a diagnostic bias, because women have a higher rate of abdominal pro-

cedures than men: incidental appendectomy is approximately five times more often performed in females compared to men throughout the reproductive years [16,18 19 20]. In contrast, the higher incidence of lung carcinoids under the age of 50 cannot be explained by the same diagnostic bias as in appendiceal carcinoids and suggests a common (hormonal) etiologic factor for all primary sites. In addition, a female predominance was also reported for gastric, colonic, and bronchopulmonary carcinoids during the first 50 years of life[16], and in the SEER database a significantly higher female/male ratio for carcinoid lesions of the appendix was observed than for malignant non-carcinoid lesions of the appendix (2.12 vs. 0.89)[21].

Not surprisingly we found that stage did matter for prognosis; five-year survival rates between stages were significantly different. These findings were in line with other reports. Modlin and Sandor presented five-year survival rates: 75-80% for localised disease, 30-35% for primary midgut carcinoid with liver metastases and 15-20% for patients with liver metastases of a hindgut or foregut primary[14].

Differences in five-year relative survival rates for localised disease between appendiceal and other gastro-intestinal carcinoids (96% vs. 88%) were not statistically significant. In contrast Sandor and Modlin found their differences (94% vs. 73%) to be significant and their result could be extended to other stages.

Treatment of patients with the carcinoid syndrome is aimed at a reduction of the incapacitating symptoms, as cure is almost never a feasible option. Since 1992, octreotide has become the main therapeutic regimen for carcinoid syndrome-related complaints in The Netherlands. Octreotide is often suggested to prolong survival but this has never been confirmed. Results from the present study might suggest that octreotide could have been a contributor to the increased survival in patients with distant metastases from midgut, lung or unknown primary site diagnosed since 1992. Virtually all patients with the carcinoid syndrome exhibit distant metastases and the majority of patients with liver metastases from midgut, lung or unknown primaries present with, or will eventually develop, the carcinoid syndrome. Therefore, patients with distant metastases from midgut, lung or unknown primary site were the best substitute for patients with the carcinoid syndrome, as expression of the carcinoid syndrome was not an item in the database of the NCR.

Treatment strategies for carcinoid disease were comparable throughout the country. The two regions with available survival data were considered representative. Multivariate analysis further emphasised the absence of regional differences in treatment strategies. Interferon-alpha was used sporadically and in trials, therefore not thought to play a major role in overall survival. As the improvement in survival in patients with metastatic carcinoid disease could also reflect a general improvement in all patients with carcinoid disease, we verified that there was only a minor, non-significant, improvement in patients with non-metastatic carcinoid disease. The study design was incapable to detect and to exclude the possible influence of earlier disease detection, stage migration, the effect of a more adequate therapy of carcinoid heart disease and the prevention of a carcinoid crisis on survival.

Improved survival in patients with metastatic disease after 1992 (confirmed by multivariate analysis) could relate to the use of octreotide and should implicate further investigation of the role of octreotide in tumour growth suppression, not only in patients with the carcinoid syndrome but also in patients with metastatic disease without the

carcinoid syndrome and, maybe, even in patients without evidence of metastatic disease.

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4.3 Incidence and survival rate of women with cervical cancer in the Greater Amsterdam area

Bulk S, Visser O, Rozendaal L, Verheijen RH, Meijer CJ. Incidence and survival rate of women with cervical cancer in the Greater Amsterdam area.
Br J Cancer. 2003 Sep 1;89(5):834-9.

ABSTRACT

Background
To evaluate the effect of population-based cervical cancer screening on the occurrence of cervical cancer in The Netherlands, we investigated the incidence and survival of cervical cancer registered by a cancer registry in the Greater Amsterdam area.
Results
The incidence rate of squamous cell carcinoma decreased significantly from 9.2/100 000 women in 1988 to 5.9/100 000 in 2000 ($P<0.001$). The incidence rate of adenocarcinomas remained stable. After adjustment for age, stage and lymph node involvement, the relative risk of death was 1.6 times higher for patients with adenocarcinomas than for patients with squamous cell carcinoma (95% CI 1.2–2.1). The decreased survival was related to histological type, as the effect remained significant after correction for confounding factors. Over time, the prognosis of women with squamous cell carcinoma improved significantly. No significant change was observed for women diagnosed with adenocarcinoma.
Conclusions
These results suggest that the screening programme in The Netherlands as executed in the Greater Amsterdam area is associated with a decreased incidence and increased survival of patients with squamous cell carcinoma, but fails to detect (pre)malignant lesions of adenocarcinoma. Since more than 92% of adenocarcinomas and its precursors contain high-risk HPV, adding HPV testing to cytological screening might improve the present screening programme in detecting adenocarcinoma and its precursor lesions.

INTRODUCTION

Population-based cervical cancer screening has led to a decrease in the incidence of cervical cancer (Gustafsson et al, 1997; Vizcaino et al, 2000). However, recent data suggest that the decrease in incidence is caused by a decrease of squamous cell carcinoma, while the incidence of adenocarcinoma of the cervix shows no change or sometimes even an increase (Anttila et al, 1999; Bergstrom et al, 1999; Hemminki et al, 2001; Liu et al, 2001).

It has been suggested that the unchanged or even increased incidence of adenocarcinoma of the cervix is the result of systematic underscreening of cervical smears for (pre)malignant changes of adenocarcinoma of the cervix (Parkin et al, 1985; Mitchell et al, 1995; Stockton et al, 1997). Moreover, patients with adenocarcinomas of the cervix are considered to have a decreased survival compared to patients with squamous cell carcinomas (Hopkins and Morley, 1991; Lai et al, 1999; Nakanishi et al, 2000; Grisaru et al, 2001). It has been suggested that this decreased survival is associated with higher stages of disease with which patients with adenocarcinomas are detected.

Here, we report on the incidence and survival rates of cervical cancer cases registered by a cancer registry in a large geographically defined region of The Netherlands, the Greater Amsterdam area. Special attention was paid to trends in incidence and survival rates for cases of squamous cell carcinoma and adenocarcinoma.

MATERIALS AND METHODS

Data collection

The cancer registry of the Comprehensive Cancer Centre Amsterdam (CCCA, 'Amsterdam Cancer Registry') is a population-based cancer registry since 1988, and part of the nationwide Netherlands Cancer Registry as of 1989. It covers two out of 12 Dutch provinces: Noord-Holland and the major part of Flevoland. The population of the CCCA region increased from 2.50 million on 1 January, 1988 to 2.80 million on 1 January, 2001. All malignant tumours were registered in all 20 hospitals in the region, comprising two university hospitals and a specialised cancer hospital (where cancer patients are treated). Clinical information and pathology data were extracted from the medical records. Apart from demographic data, data were collected on tumour site, morphological classification (according to the International Classification of Diseases for Oncology) and stage of the tumour. The fourth edition of the TNM-classification was used whenever applicable (Hermanek and Sobon, 1987). In 1988–1993, the FIGO stage was registered separately, and after 1993 the FIGO stage was derived from TNM stage. Data concerning participation in cervical cancer screening programmes were not available.

For this study, all cervical cancer cases diagnosed between 1 January, 1988 and 31 December, 2000 were selected from the cancer registry. The following tumours were excluded: non-invasive tumours and tumours diagnosed in patients living outside the CCCA region. Patients diagnosed in a hospital outside the region, but living in the CCCA region were included. Information on the vital status of all patients was collected

in the hospitals and from general practitioners. However, the majority of the information on vital status was obtained from record linkage of computerised data on all deceased persons in the study period that were made available by 51 of the 74 municipalities in the CCCA region (covering more than 85% of the population). Inquiries about the vital status of patients living in the other 23 municipalities were made at the municipal population registers and at the Central Office for Genealogy of The Netherlands, The Hague. Less than 1% of the cases were lost to follow-up. In the survival analyses, cases diagnosed in 1998–2000 were excluded, because of the short period of follow-up. Tumours first diagnosed at autopsy, second (or third, etc.) tumours and non-carcinomas were also excluded from the survival analyses. Follow-up of the patients diagnosed in 1988–1997 was complete until at least 1 January, 1999.
Population data of The Netherlands were obtained from Statistics Netherlands (CBS, Voorburg/Heerlen, The Netherlands). Data from Statistics Netherlands were also obtained with respect to the survival of the general Dutch population.

Statistical analysis

Incidence of cervical cancer was calculated per 100 000 person years. Direct standardisation was used for age adjustment with respect to the European standard population, and the European standardised rates (ESRs) were calculated. Trends in the incidence of the ESR were investigated by calculating the estimated annual percent change (EAPC) (Visser et al, 2001). For the analyses, cases were divided into squamous cell carcinoma, adenocarcinoma including adenosquamous carcinoma and other histological type (i.e., other and unspecified carcinomas, sarcomas and undefined tumours). Age was divided into 15-year categories. However, age categories of 15–29 and 30–44 years were analysed jointly in the survival analyses, based on the low number of cases (n=90) in the category of 15–29 years. Differences in distribution over stage and age categories were assessed with X2 statistics.
Relative survival and 95% confidence intervals (CIs) were calculated as a measure of disease-specific survival (Hakulinen and Abeywickrama, 1985). The relative survival is the ratio between crude and expected survival and is close to disease-specific survival. We did not calculate disease-specific survival, because the cause of death was not available as linkage with the death registry in The Netherlands is not possible.
The Cox multivariate regression analysis for survival was performed to investigate survival. Associations were examined for all cases, and for cases of squamous cell carcinoma and adenocarcinoma separately. In the analyses, the FIGO classification was used to adjust for stage. Lymph node status is not considered in the FIGO classification for cervical carcinoma, and therefore it was introduced in the analyses as a separate variable. For cases diagnosed in 1988, TNM was not registered, so these cases were classified as 'nodal involvement unknown'. Age, stage and nodal involvement were divided into categories and entered into the model as dummy variables. P-values of 0.05 or less were considered statistically significant. Using STATA 6.0 for Windows, hazard ratios (HRs) and 95% CIs were calculated.

RESULTS

From 1988 up to 2000, 1925 patients were diagnosed with invasive cervical cancer (Table 1). The annual number of incident cases of cervical cancer decreased from 157 patients registered in 1988 to 135 patients in 2000. The ESR decreased from 11.8/100000 women in 1988 to 8.2/100 000 women in 2000. The total ESR decreased by 2.7% annually (P<0.001). This decrease in incidence was mainly caused by a decrease in the incidence of squamous cell carcinoma cases, as the EAPC in ESR for squamous cell carcinomas was -3.2% (P<0.001). For adenocarcinomas, there was no statistically significant trend in the incidence (EAPC -1.1%, P=0.54). The incidence of other cervical malignancies decreased with 1.4% annually (P=0.74). During the study period, the contribution of adenocarcinomas to the total number of malignancies increased from 16% in 1988–1990 to 18% in 1998–2000.

Table 1. Incidence of cervical cancer in the Greater Amsterdam area, the Netherlands, 1988–2000

	SCC		*AdCx*		*Other*		*Total*	
Year	*Cases*	*ESR*	*Cases*	*ESR*	*Cases*	*ESR*	*Cases*	*ESR*
1988	128	9.7	22	1.6	7	0.5	157	11.8
1989	129	9.5	24	1.8	2	0.2	155	11.5
1990	125	8.8	29	2.2	4	0.3	158	11.3
1991	111	7.6	19	1.2	4	0.3	134	9.0
1992	134	9.5	28	1.9	6	0.4	168	11.9
1993	126	8.9	30	2.1	2	0.2	158	11.1
1994	114	7.5	26	1.8	4	0.3	144	9.6
1995	120	7.8	25	1.7	3	0.2	148	9.7
1996	107	6.8	18	1.2	7	0.4	132	8.5
1997	117	7.4	32	2.1	4	0.2	153	9.6
1998	118	7.5	33	2.1	2	0.1	153	9.6
1999	108	6.8	17	1.1	5	0.3	130	8.2
2000	100	6.1	26	1.6	9	0.6	135	8.2
EAPC		-3.2%		-1.1%		-1.4%		-2.7%
P-value		<0.001		0.54		0.74		0.001

SCC=squamous cell carcinoma; AdCx=adeno(squamous)carcinoma; ESR=European standardised rate; EAPC=estimated annual percent change

The median age of patients with adenocarcinoma was 3 years below the median age of patients with squamous cell carcinoma, that is 44 years (range: 18–92) and 47 years (range: 19–98), respectively (P<0.05). Age-specific incidence was highest in age groups 35–39 and 70–84 years for squamous cell carcinoma patients, and the age-specific incidence was highest in the age group 35–49 years for adenocarcinoma patients (Figure 1).

Younger patients were more often diagnosed in early stages of cancer than older patients (Figure 2). Of women 15–29 years, 82% were diagnosed with FIGO stage I disease, while only 15% of patients 75 years and over were diagnosed with FIGO stage I disease. Only 2% of the patients in the age category 15–29 years were diagnosed in stage IV, while 14% of the oldest patients were diagnosed in this stage. Figure 3 shows that 55% of squamous cell carcinomas and 65% of patients with adenocarci-

nomas were diagnosed in FIGO stage I (P=0.003). However, adenocarcinomas were diagnosed less often in the microinvasive (i.e., Ia) stage of the disease than squamous cell carcinomas (15 and 22%, respectively) (P<0.0001). The percentage of cases diagnosed in FIGO stage IV did not differ statistically significantly between squamous cell carcinomas (7%) and adenocarcinomas (6%) (P=0.71). During the study period, there were no statistically significant changes in distribution over the stages.

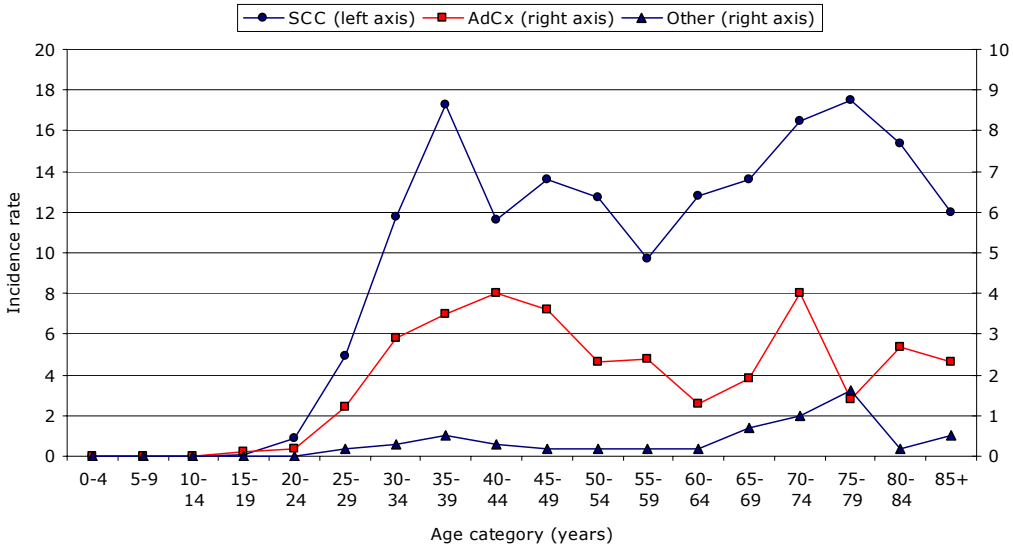

Figure 6. Age-specific incidence rates by histological type of patients in the Greater Amsterdam area 1988–2000.

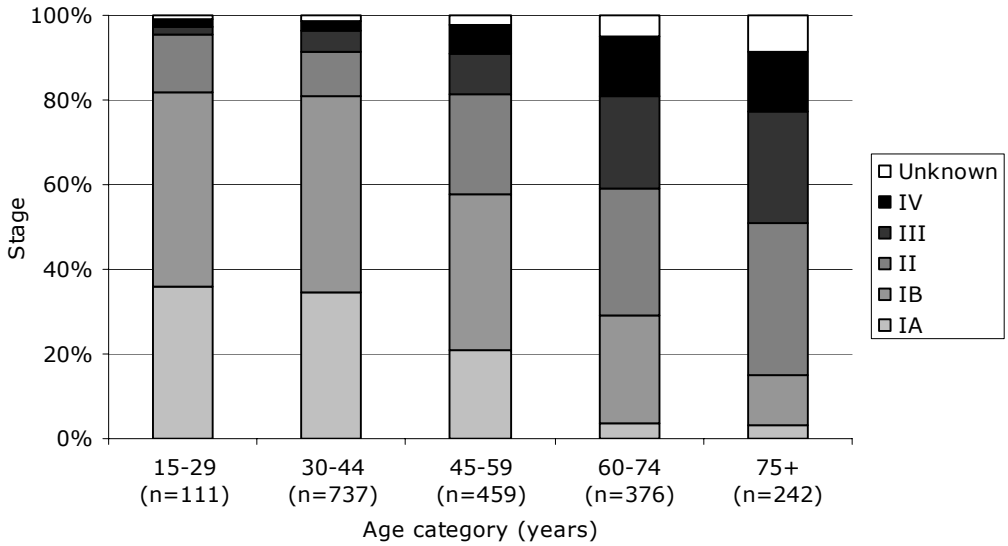

Figure 7. Stage at diagnosis by 15-year age category of patients in the Greater Amsterdam area, the Netherlands, 1988–2000.

During 1988–1997, there were 1441 patients with cervical carcinoma in the region of the CCCA, 480 of whom died (33.3%). The median follow-up time was 56 months (range: 0–165 months). The overall 5-year relative survival of cervical carcinoma was 71% (Table 2). Relative survival decreased from 85% for women o45 years to 41% for women of 75 years and over. Patients with FIGO stage I had a relative survival of 91% decreasing to 16% for tumours diagnosed in FIGO stage IV. Relative survival of squamous cell carcinomas was 72% (95% CI: 69–75%), and somewhat lower for adeno(squamous) carcinomas (66%, 95% CI: 59–72%).

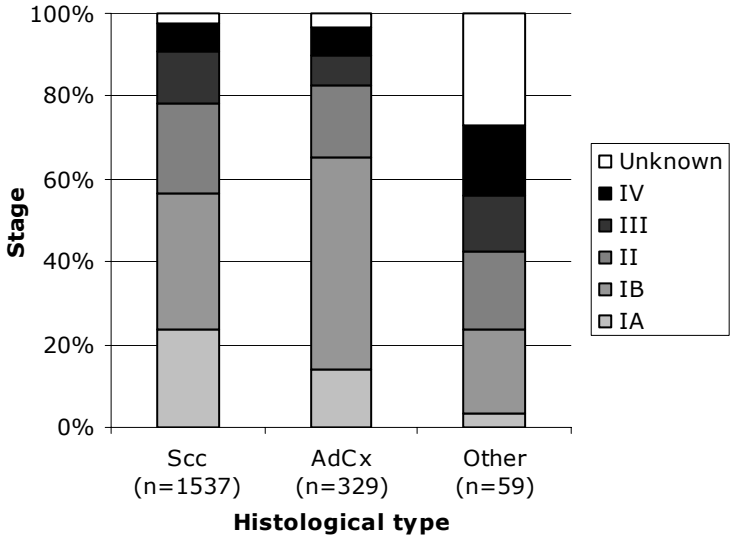

Figure 8. Stage at diagnosis by histological type of patients in the Greater Amsterdam area, the Netherlands, 1988-2000

Table 2. Relative survival of patients with cervical carcinoma in the Greater Amsterdam area, the Netherlands in 1988-1997

Variable	*Category*	*Cases*	*5-year survival (%)*	*95% CI (%)*
All cases		1 441	71	68-74
Age	<45	665	85	82-88
	45-59	321	72	66-77
	60-74	285	54	47-60
	75+	170	41	31-52
FIGO stage	I	831	91	88-93
	II	304	57	50-64
	III	168	35	27-43
	IV	99	16	9-24
	Unknown	39	44	27-61
Histology	SCC	1 169	72	69-75
	AdCx	244	66	59-72
	Other/unspecified carcinoma	28	60	38-78

CI=confidence interval; SCC=squamous cell carcinoma; AdCx=adeno(squamous)carcinoma

Table 3 displays the results of the multivariate analysis of survival for all types of cervical cancer. Compared to FIGO stage I, all other stages had significantly increased HRs. Lymph node status is not considered in the FIGO classification for cervical carcinoma. For cases diagnosed in 1988, TNM was not registered and these cases were classified as 'nodal involvement unknown'. However, nodal involvement appeared to be associated with an increased risk of death (HR 2.1, 95% CI 1.6–2.7). Tumour histology was investigated with squamous cell carcinoma cases as reference category. Univariately, the HR of adenocarcinomas was slightly increased (HR 1.1), while other/unspecified carcinomas were associated with a significant increase in risk. The increased risk for other/unspecified carcinomas disappeared with multivariate adjustment, indicating that the increase in risk was caused by confounding by age and stage. After adjustment, the HR for adenocarcinomas was significantly increased (HR 1.6, 95% CI 1.3–2.1). Over time, the prognosis of patients with cervical cancer improved, as the multivariate HRs were decreased for the periods 1991–1993 and 1994–1997 as compared to the reference period 1988–1990. Adjustment for stages 1a and 1b separately did not alter these findings substantially (data not shown).

Table 3. Relative risk of death for patients in the Greater Amsterdam area, The Netherlands, with cervix carcinoma diagnosed in 1988–1997 (n=1441)

		Univariate		*Multivariate*[a]	
Factor	*Cases*	*Hazard ratio*	*95% CI*	*Hazard ratio*	*95% CI*
FIGO stage					
I	831	1	Reference	1	Reference
II	304	4.9*	3.8-6.3	3.3*	2.6-4.7
III	169	10*	7.9-13	6.4*	4.7-8.5
IV	99	19*	14-25	11*	7.6-15
Unknown	39	9.2*	5.9-14	5.7*	3.6-9.1
Nodal involvement					
No	563	1	Reference	1	Reference
Yes	668	3.2*	2.5-4.1	2.1*	1.6-2.7
Unknown[b]	210	1.6*	1.3-2.0	1.4*	1.1-1.8
Morphological type					
SCC	1 169	1	Reference	1	Reference
AdCx	244	1.1	0.9-1.4	1.6*	1.3-2.1
Other/unspecified carcinoma	28	1.7	1.0-3.0	0.7	0.4-1.2
Year of diagnosis					
1988/1990	451	1	Reference	1	Reference
1991/1993	442	0.7*	0.6-0.9	0.8*	0.6-1.0
1994/1997	548	0.8	0.7-1.1	0.8*	0.6-1.0

[a] Adjusted for age category and all other factors in the table.
[b] Cases diagnosed in 1988 were all classified as unknown.
*P<0.05. CI=confidence interval; SCC=squamous cell carcinoma; AdCx=adeno(squamous)carcinoma.

Squamous cell carcinoma cases and adenocarcinoma cases were also analysed separately (Table 4). Both for squamous cell carcinomas and adenocarcinomas, survival decreased with increasing age, higher FIGO stage and positive lymph nodes at diagnosis (data not shown). The improvement in survival of women with cervical cancer dur-

ing the period 1988–1997 was associated with cases of squamous cell carcinoma only. Survival of women with cervical adenocarcinoma did not improve during the study period (Table 4).

Table 4. Relative risk of death for patients in the Greater Amsterdam area, The Netherlands, with cervix carcinoma diagnosed in 1988–1997 (n=1441). Year of diagnosis as an indicator of survival, separately for patients with squamous cell carcinoma and adenocarcinoma

		Univariate		*Multivariate*[a]	
Factor		*Hazard ratio*	*95% CI*	*Hazard ratio*	*95% CI*
Year of diagnosis AdCx	1988/1990	1	Reference	1	Reference
	1991/1993	0.9	0.5-1.5	0.8	0.5-1.5
	1994/1997	1.0	0.6-1.6	1.2	0.7-2.0
Year of diagnosis SCC	1988/1990	1	Reference	1	Reference
	1991/1993	0.7*	0.6-0.9	0.8*	0.6-1.0
	1994/1997	0.8	0.6-1.0	0.8*	0.6-1.0

[a]Adjusted for age, stage and nodal involvement.
*P<0.05. CI=confidence interval; SCC=squamous cell carcinoma; AdCx=adeno(squamous)carcinoma.

DISCUSSION

Our results show that the incidence of cervical cancer has decreased significantly during the period 1988–2000, and that this decrease is caused by a decrease in the incidence of squamous cell carcinomas. In multivariate analyses, survival for patients diagnosed with adenocarcinoma of the cervix was significantly lower than survival for patients with squamous cell carcinoma. This indicates that women with adenocarcinoma of the uterine cervix have an intrinsically increased risk of death compared with women with squamous cell carcinoma independent of stage, age and nodal involvement.

We studied patients with cervical cancer who were all diagnosed within a geographically defined region in The Netherlands: the Greater Amsterdam area. As data were obtained by the Regional Cancer Registry, we were able to study an unbiased population of women with different histological types of cervical cancer for factors associated with survival. In this study, the histological verification rate was 99.8%. Nationally, the histological verification-rate for cervical cancer is 99.7%, indicating a high accuracy rate of the Dutch Cancer Registries (Visser et al, 1997).

In this study, knowledge of participation in cervical cancer screening preceding the diagnosis of cancer may have been relevant. We did not have data on either individual Pap smear taking or participation in the nationwide screening programme in this group of women with cervical carcinoma. Cytological screening on an individual basis has been available for women in this region of The Netherlands since the 1970s. A nationwide screening programme aimed at specific age categories was initiated in 1988.

Between 1988 and 1996, women aged 34–54 years were screened triannually, and from 1996 onwards, women aged 30–60 years are screened every 5 years. Overall, the coverage of cervical cancer screening activities over a period of 5 years is approximately 80% (van Ballegooijen and Hermens, 2000). However, regional participation in each screening round of the population-based programme is lower (60–70%). Even without data on screening participation, some findings do suggest the efficacy of

screening in this region of The Netherlands. The incidence of cervical squamous cell carcinoma decreased significantly, while no statistically significant change in the incidence of adenocarcinoma was found. Previous studies have reported that cervical adenocarcinoma and its preinvasive stages are diagnosed less efficiently by Pap smear screening than squamous cell lesions (Mitchell et al, 1995; Stockton et al, 1997). In some countries, not only the absence of a decrease in incidence (Sigurdsson, 1993; Nieminen et al, 1995), but also increases in the incidence of cervical adenocarcinoma have been described in the presence of a screening programme (Bergstrom et al, 1999; Hemminki et al, 2001; Liu et al, 2001). One study even suggested an increase in incidence especially in younger women (Anttila et al, 1999), whereas older women were not affected by increases in the incidence rate of cervical cancer. Our data do not support this trend. Our findings suggest a positive effect of the screening programme as shown by the decrease in cervical carcinoma incidence. Increasing screening participation to obtain an even higher degree of coverage will most likely increase the efficacy of the screening programme in decreasing the incidence of cervical cancer. In our analyses, patients with cervical adenocarcinoma had a worse prognosis than patients with squamous cell carcinoma after correction for confounders such as age, stage and nodal involvement. Previous studies either usually lacked sufficient numbers of patients with adenocarcinomas (Pilch et al, 2001), or were not population-based (Hopkins and Morley, 1991; Nakanishi et al, 2000), or did not make direct comparisons between patients with squamous cell carcinoma and adenocarcinoma (Benedet et al, 1998). Some studies attributed the decreased survival of women with adenocarcinoma to differences in histological type (Lai et al, 1999; Grisaru et al, 2001). In our study, patients with adenocarcinoma presented with more advanced stage I tumours than patients with squamous cell carcinomas. Still, patients with cervical adenocarcinoma were slightly younger at diagnosis than patients with squamous cell carcinoma, 48 and 50 years, respectively. As the association between adenocarcinomas and a worse prognosis increased after correction for confounding factors, this indicates that women with cervical adenocarcinoma have an inherently worse prognosis than women with squamous cell carcinoma. The main causal factor for the development of both squamous cell carcinoma and adenocarcinoma of the uterine cervix is infection with high-risk types of the human papillomavirus (hrHPV) (Walboomers et al, 1999; Bosch et al, 2002). There are substantial differences with respect to the exact type of hrHPV and the histological diagnosis. Adenocarcinomas are more often associated with HPV type 18 than squamous cell carcinomas (Bosch et al, 1995, 2002; Andersson et al, 2001; Clifford et al, 2003). Moreover, HPV 18 has been shown to be associated with a worse prognosis than other HPV types (Hildesheim et al, 1999; Schwartz et al, 2001), but this finding has been challenged (Pilch et al, 2001). An intrinsic difference between neoplasically converted squamous and cylindrical epithelium might also be the cause of the difference in prognosis, independent of HPV infection.

The survival of patients with squamous cell carcinoma increased during 1988–1997, while the survival of patients with adenocarcinomas did not change significantly. During the study period, there were no large changes in treatment of patients with cervical cancer in any stage of the disease. The nationwide screening programme was introduced in 1988. Theoretically, an improvement in the prognosis of patients with squamous cell carcinomas might have been caused by a major change in stage at di-

agnosis during the study period. We did not observe such a change in stage at diagnosis over time (data not shown). However, we cannot exclude an effect of subtle changes within broad stages, such as a shift from FIGO 1b to FIGO 1a. Screening, leading to an earlier detection of cervical cancer even without significant changes in broad FIGO stage distribution, may contribute to such an effect. We were not able to find a trend over time in histological lymph node positivity over all stages of disease, as lymph node sampling is dependent on stage at diagnosis. In this study, in 31% of women with adenocarcinoma and 43% of women with squamous cell carcinoma, lymph node status was not determined histologically. Stage migration due to improved staging procedures might also have contributed to the increased survival. Still, the statistically significant difference in survival was based on small numbers of adenocarcinoma cases compared to squamous cell carcinoma cases. Therefore, caution should be taken into account when interpreting trends in the survival of adenocarcinoma based on these data.

The overall 5-year survival rate was 71%. Compared to other countries in Europe, this is a high survival rate, with only the Nordic countries having comparable survival rates (Berrino et al, 1999). Other studies have also shown that within Europe, The Netherlands have a very low incidence, and a very high survival compared with other countries (Levi et al, 2000). It is reasonable to attribute these findings to the presence of a nationwide screening programme, as similar effects on incidence have been described in other countries with a screening programme (Gustafsson et al, 1997). Whether the effect on survival in the absence of changes in treatment can be exclusively attributed to the cervical cancer screening programme, remains a question of debate (Quinn et al, 1999; Sasieni and Adams, 1999).

Our study suggests that the present screening programme for cervical cancer is efficient in detecting (pre) malignant stages of squamous cell carcinoma, but fails to detect (pre) malignant stages of adenocarcinoma (Sasieni and Adams, 2001). Since more than 92% of the adenocarcinomas and its precursors contain hrHPV (Pirog et al, 2000; Pilch et al, 2001), adding hrHPV testing to conventional cytological screening might improve the present screening programme in detecting adenocarcinoma and its precursor lesions. This should be a focus of further research concerning the functioning of the screening programme for cervical cancer.

In conclusion, in the Greater Amsterdam area, the incidence of squamous cell carcinomas has decreased while there were no changes in the incidence of adenocarcinoma of the uterine cervix. Cases of adenocarcinoma of the uterine cervix are associated with a decreased survival rate compared to patients with squamous cell carcinoma. This decreased survival is related to tumour histology itself, since after correction for factors such as age, stage and lymph node status, the survival of adenocarcinoma patients is still lower compared with squamous cell carcinoma patients.

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4.4 Local recurrence after cystectomy and survival of bladder cancer patients: a population based study in Greater Amsterdam

Visser O, Nieuwenhuijzen JA, Horenblas S; MEMBERS of the UROLOGICAL ONCOLOGY WORKING GROUP of the COMPREHENSIVE CANCER CENTRE AMSTERDAM. Local recurrence after cystectomy and survival of bladder cancer patients: a population based study in Greater Amsterdam.
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ABSTRACT

Objectives
To determine retrospectively in a population based study the survival of patients with bladder cancer and the local recurrence rate (LRR) after cystectomy.
Methods
All bladder cancer cases diagnosed between 1988 and 2001 (vital status updated until September 2003) were selected from the Amsterdam Cancer Registry, which covers a population of 2.84 million people. For all patients who underwent a cystectomy between 1988 and 1997 in 18 participating hospitals, information on local recurrence and the vital status was collected from the medical records.
Results
Five-year relative survival for all bladder cancer cases combined (n=8 321) was 75%. For clinical stage 0-a this was 99%, decreasing to 85% for stage 0-is and 82% for stage I, and to 44%, 28% and 9% for stages II, III and IV, respectively. Five-year relative survival after cystectomy was 81%, 44% and 23% for stages II, III and IV, respectively. The LRR after cystectomy (n=566) was 19% for all cases and institutions combined. The LRR increased with higher pT-stages and reached 11%, 23% and 31% for stage II, III and IV respectively, and was slightly lower in oncological centers (18%) than in community hospitals (20%) (not significant).
Conclusions
Survival is higher than the European average, but below the figure for the United States. Only one in three stage II-III patients was treated with cystectomy. A relatively high stage-specific survival is experienced after cystectomy, in spite of a local recurrence in 1 out of 5 patients.

INTRODUCTION

Bladder cancer is the sixth cancer in the Netherlands.[1] Compared to other European countries, the incidence of bladder cancer is relatively low.[2] In the Netherlands, more than two-thirds of all new bladder cancer patients present with superficial disease[3], which can be sufficiently treated with (repeated) local treatments. A cystectomy is usually offered as treatment of first choice to patients presenting with muscle invasive bladder cancer and to patients in whom local treatment of superficial bladder cancer is unsuccessful. Studies on the local recurrence after cystectomy are often hospital-based and local recurrence rates (LRR) have been reported from 7% to 25%.[4-7]
This study aims to investigate in a population-based setting the survival of bladder cancer patients and the LRR after cystectomy in the region of the Comprehensive Cancer Centre Amsterdam (CCCA).

MATERIALS AND METHODS

Cancer registry data

All primary bladder tumors diagnosed in patients with residence in the CCCA-region (population: 2.84 million) between January 1st 1988 and December 31st 2001 were selected from the Amsterdam Cancer Registry, a population-based cancer registry with complete regional coverage. Registration clerks extract information for the registry from detailed hospital records. Apart from demographic data, data are collected on morphology, stage and primary treatment. Stage grouping in this study was according to the 5th edition of the TNM-classification (table 1).[8] cTNM was used for the survival analysis which included all patients, pTNM was used in a subset analysis of cystectomy cases. We converted older TNM-data to the 5th edition. All T4-tumors were classified as stage IV, because the sub-classification into T4a/b was not available for all cases.

Table 1. Stage grouping according to the 5th edition of the TNM-classification

Stage	tumour	lymph nodes	metastasis
0-a	Ta	N0	M0
0-is	Tis	N0	M0
I	T1	N0	M0
II	T2a, b	N0	M0
III	T3a, b	N0	M0
	T4a	N0	M0
IV	T4b	N0	M0
	Any T	N1, N2, N3	M0
	Any T	Any N	M1

Follow-up

The vital status of all patients was updated by linking files with deceased persons to the cancer registry. These electronic data files, covering 1988-1999, were made available by the majority of the municipal population registers and included all deceased residents (irrespective of cause of death). Active follow-up in the hospitals was performed for patients residing in the remaining municipalities and if electronic data did not fully cover 1988-1999. Subsequently, the vital status of all patients still alive at last

follow-up was updated until September 1st 2003 by linkage to the electronic death register of the Central Office for Genealogy (COG), which contains all deceased Dutch residents from October 1st 1994. This register is updated on a daily basis with data from all municipal population registers in the Netherlands. Patients whose follow-up ended before October 1st 1994 were checked in the personal record card register of the CBG, containing all deceased Dutch residents before October 1st 1994. Finally, patients not known by COG were assumed to be alive at September 1st 2003. Completeness of follow-up is estimated to be over 99.5%.[9]

Cystectomy

A subset of patients was defined by selecting patients from the cancer registry who underwent cystectomy during 1988-1997. Data from two small hospitals (out of 20) could not be included, because one hospital refused permission to extract data from the medical records, and because many patient-files had been destroyed in another. Patients referred to the oncological centers from outside the CCCA-region were excluded to keep data population based. Patients for whom cystectomy was not the primary treatment were included, but in several hospitals these cases could not be included because of missing data in the medical records department.
A supplementary data set including date of surgery, intent of the surgery (curative or palliative), presence of residual disease after surgery, and the occurrence and date of local recurrence (i.e. recurrence in the soft tissue within the true pelvis) was extracted from medical records. In case the cystectomy was not the primary treatment, TNM and morphology at date of cystectomy were also registered. Patients were followed at least 5 years after cystectomy.

Statistical methods

Because the cause of death is not available in the population registers, we were unable to calculate disease specific survival. Instead, we calculated relative survival using STATA according to Dickman *et al*.[10] This method corrects crude survival for expected mortality according to annual life tables of the general population.
For the comparison of LRR between hospitals a standardized LRR was calculated. Based on the stage-specific LRR for all hospitals combined and the stage distribution in a specific hospital, an expected number of local recurrences was calculated for each hospital. The expected numbers were compared with the observed numbers and a stage-standardized local recurrence ratio (SLRR) was calculated as the ratio between the observed and expected numbers. Exact 95% confidence intervals (CI) based on the Poisson distribution of O, and Kaplan-Meier survival curves were calculated using STATA.

RESULTS

Primary treatment of patients with primary bladder cancer

A total of 8 321 patients with primary bladder cancer were diagnosed between 1988-2001. About three quarters of all patients received local treatment only as primary

treatment (table 2). Of the patients presenting with clinical stage II and III, 33% and 24% received local treatment. In clinical stage II and III, more patients underwent radiotherapy (36% and 40%, respectively) than cystectomy (30%). Patient of 75 years or older underwent cystectomy less often than younger patients (chi^2-test: p<0.001).

Table 2. Primary treatment of primary bladder cancer in Greater Amsterdam, 1988-2001

cTNM-stage/ age group*	Number of patients	Primary treatment (%)			
		Local treatment only	Cystectomy (with or without radiotherapy)	Radiotherapy	Other
0-a	3 698	98%	<1%	<1%	2%
0-is	191	88%	2%	1%	9%
I	1 914	90%	3%	5%	2%
II	1 170	33%	30%	36%	1%
< 75 years	711	22%	44%	33%	<1%
75 or older	459	51%	6%	41%	1%
III	457	24%	30%	40%	7%
< 75 years	253	15%	44%	35%	5%
75 or older	204	36%	9%	46%	9%
IV	572	42%	11%	29%	18%
Unknown	240	31%	24%	13%	33%
Not applicable	79	28%	4%	3%	66%
Total	8 321	76%	8%	11%	5%

* stage grouping according to the 5th edition of the TNM Classification [8], but T4 classified as stage IV

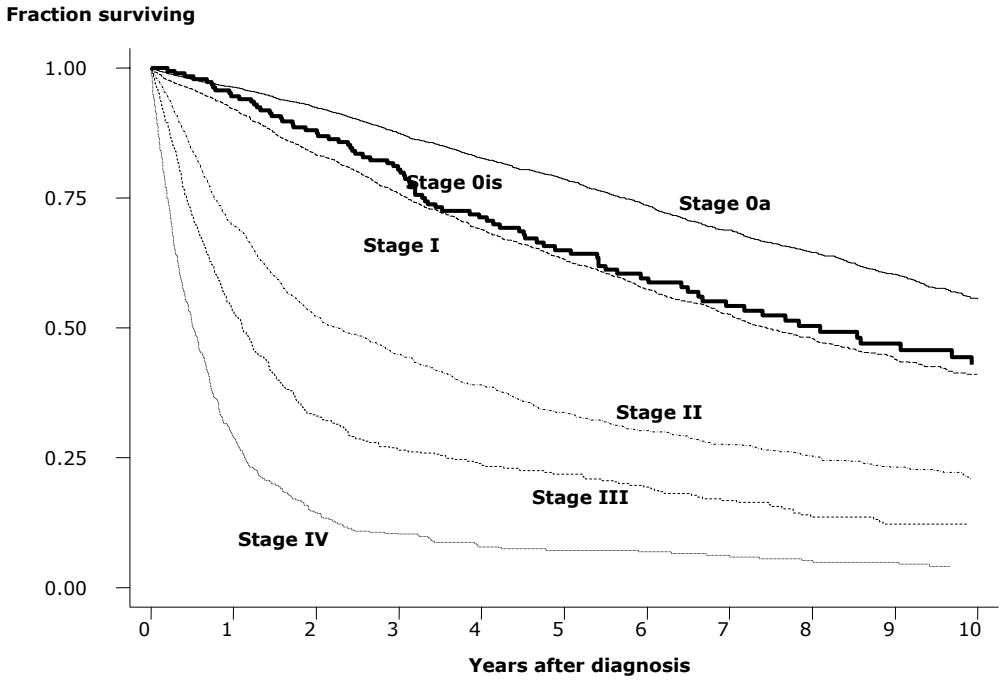

Figure 1. Crude survival according to clinical stage at diagnosis of bladder cancer patients in Greater Amsterdam, 1988-2001

Survival for all patients

One- and five-year crude survival of all patients combined was 83% and 58%. Crude survival according to stage is shown in figure 1. The one- and five-year relative survival rate (RSR) was 87% and 75% (table 3). The ten-year RSR was 67% (95% CI: 65-70%). The RSRs decrease with increasing age.

Table 3. Relative survival (%) of bladder cancer patients in Greater Amsterdam, 1988-2001

Parameter	Number of cases	Years after diagnosis (95% confidence interval) 1	5	10
Period of diagnosis				
- 1988-1991	2 182	88 (86-90)	75 (72-77)	67 (63-70)
- 1992-1995	2 453	86 (85-88)	76 (74-79)	69 (65-72)
- 1996-1998	1 809	86 (84-88)	73 (71-76)	
- 1999-2001	1 877	88 (86-90)		
Sex				
- Males	6 560	89 (88-90)	76 (75-78)	69 (66-71)
- Females	1 761	80 (78-82)	70 (67-73)	63 (58-67)
*Age group**				
- 15-44	251	95 (92-97)	90 (85-93)	86 (80-90)
- 45-54	738	94 (92-96)	86 (83-88)	80 (75-83)
- 55-64	1 690	92 (90-93)	79 (77-81)	73 (70-76)
- 65-74	2 905	88 (87-89)	76 (73-78)	67 (63-70)
- 75+	2 733	80 (78-82)	66 (63-70)	56 (49-63)
*cTNM- stage***				
- 0-a	3 698	101 (100-101)	99 (97-101)	92 (88-95)
- 0-is	191	99 (95-102)	85 (75-94)	78 (61-93)
- I	1 914	97 (95-98)	82 (79-85)	73 (68-78)
- II	1 170	74 (71-77)	44 (40-48)	36 (31-41)
- III	457	56 (51-61)	28 (23-34)	21 (16-28)
- IV	572	30 (26-34)	9 (6-12)	6 (3-9)
- Unknown	240	68 (61-75)	49 (40-57)	37 (26-49)
- TNM not applicable	79	37 (26-48)	22 (12-34)	14 (6-28)
Morphological type				
- Transitional cell ca.	7 973	89 (88-90)	77 (76-79)	70 (67-72)
- Squamous cell ca.	113	38 (29-47)	23 (14-32)	18 (8-31)
- Adenocarcinoma	76	70 (58-80)	38 (26-51)	21 (10-36)
- Undifferentiated ca.	82	37 (27-48)	14 (6-25)	11 (3-25)
- Sarcoma	19	65 (39-83)	29 (10-53)	22 (6-47)
- Unknown***	58	27 (16-40)	18 (8-32)	15 (5-31)
Morphological grade				
- Grade 1	1 626	101 (99-101)	101 (98-103)	94 (89-99)
- Grade 2	2 594	96 (95-97)	88 (86-90)	80 (76-84)
- Grade 3	2 858	75 (73-77)	52 (50-55)	43 (39-47)
- Grade 4	191	44 (37-52)	26 (19-34)	19 (11-29)
- Grade unknown	1 052	84 (82-87)	73 (69-77)	66 (61-72)
Total	8 321	87 (86-88)	75 (74-76)	67 (65-70)

* 4 cases 0-14 year
** stage grouping according to the 5th edition of the TNM Classification [8], but T4 classified as stage IV
*** no pathological confirmation

For females, the RSR after five and ten years was 6% lower than for males. This was caused by a less favorable stage distribution in females (14% of all females were diagnosed as clinical stage II, 7% stage III, and 10% stage IV, compared to 14% stage II, 5% stage III, and 6% stage IV in males). Stage-specific RSRs in females (five-year RSRs of 79%, 42% and 16% for stage I, II and III, respectively) were also lower than in males (five-year RSRs of 83%, 44% and 33% for stage I, II and III). Survival for patients diagnosed between 1999-2001 was almost equal to survival of patients diagnosed about 10 years earlier (1988-1991).
Up to five years after diagnosis, patients with stage 0-a bladder cancer experienced a survival almost equal to the general population (RSR: 99%, CI: 97-101%), but the ten-year RSR was 92% (CI: 88-95%). For patients with stage 0-is and stage I five-year RSRs (85% and 82%, respectively) and ten-year RSRs (78% and 73%) were almost equal.
Patients with muscle-invasive bladder cancer experienced five-year survival decreasing from 44% for stage II, to 28% for stage III, and 9% for stage IV. The ten-year RSR was 36%, 21% and 6% for stage II, III and IV. Adenocarcinoma, squamous cell carcinoma and undifferentiated carcinoma of the bladder resulted in lower survival figures than transitional cell carcinoma (table 3). The five-year RSR for grade I tumors was 101%, decreasing to 88% for grade II, 52% for grade III and 26% for grade IV.

Table 4. Local recurrence rate after cystectomy for bladder cancer in Greater Amsterdam, 1988-1997 (cystectomies with palliative intent and/or macroscopic residual disease excluded)

Parameter	Number of cystectomies	Local recurrence			
		Yes (%)	Odds Ratio	No (%)	Unknown (%)
Sex					
- Males	448	85 (19)	1 (Ref.)	355 (79)	8 (2)
- Females	118	25 (21)	1.0 (0.6-1.8)	88 (75)	5 (4)
Morphological type					
- Transitional cell ca.	214	97 (19)	1 (Ref.)	406 (79)	11 (2)
- Squamous cell ca.	27	3 (11)	0.4 (0.1-1.4)	22 (81)	2 (7)
- Adenocarcinoma	18	7 (39)	2.4 (0.8-6.7)	11 (61)	-
- Undifferentiated ca.	7	3 (43)	2.4 (0.5-11)	4 (57)	-
*pTNM- stage**					
- 0 (Ta/Tis)	22	1 (5)	}1 (Ref.)	21 (95)	-
- I	74	11 (15)		63 (85)	-
- II	123	13 (11)	0.8 (0.4-2.0)	110 (89)	-
- III	258	59 (23)	2.2 (1.1-4.4)	189 (73)	10 (4)
- IV	83	26 (31)	3.0 (1.4-6.7)	54 (65)	3 (4)
- Unknown	6	-		6 (100)	-
*Residual disease***					
- R0	490	90 (18)	1 (Ref.)	395 (81)	5 (1)
- R1	42	13 (31)	1.4 (0.7-2.9)	27 (64)	2 (5)
- RX	34	7 (21)	1.0 (0.4-2.3)	21 (62)	6 (18)
Hospital					
- Community hospital	458	91 (20)	1 (Ref.)	354 (77)	13 (3)
- Oncological centre	108	19 (18)	0.8 (0.5-1.5)	89 (82)	-
Total	566	110 (19)		443 (78)	13 (2)

* stage grouping according to the 5th edition of the TNM Classification [8], but T4 classified as stage IV
** R0 = no residual disease; R1 = microscopic residual disease; RX = unknown

Local recurrence after cystectomy

577 patients underwent a cystectomy between 1988-1997 (number of cystectomies per hospital/year: 0-12), of whom eleven had macroscopic residual disease (three stage III, eight stage IV tumors). In 110 (19%) of the remaining 566 patients a local recurrence occurred (table 4). Of thirteen patients medical records were not accessible and it could not be established whether a local recurrence had occurred. Most of them died within a year after cystectomy.
There was little difference in the LRR between males and females (19% and 21%, respectively). The LRR was decreased for squamous cell carcinoma compared to transitional cell carcinomas. For adenocarcinomas and undifferentiated carcinomas the LRR was increased (not significant). For the lower stages, the LRR was 5% in stage 0-a/0-is, 15% in stage I, and 11% in stage II. For stage III (LRR 23%, odds ratio 2.2, CI 1.1–4.4) and stage IV bladder cancer (LRR 31%, odds ratio 3.0, CI 1.4–6.7) the LRRs were significantly increased. The presence of microscopic residual disease after cystectomy was an unfavorable factor (odds ratio 1.4, CI 0.7-2.9). In patients who underwent cystectomy in an oncological centre the LRR was lower than for patients from community hospitals, but the difference was not statistically significant. Figure 2 shows that the SLRR for the various hospitals ranged from 0 to 1.7 (all hospitals combined: 1), but for all hospitals the CI included 1.
Figure 3 shows survival of patients after cystectomy. Crude 5-year survival of patients with local recurrence was 11% (median 15 months), without local recurrence 63% (log-rank: $p<0.0001$). The difference in survival between patients with and without local recurrence was mainly caused by the poor survival after local recurrence: median survival after local recurrence was only 2.5 months, while 1-year survival was 19% (figure 4).

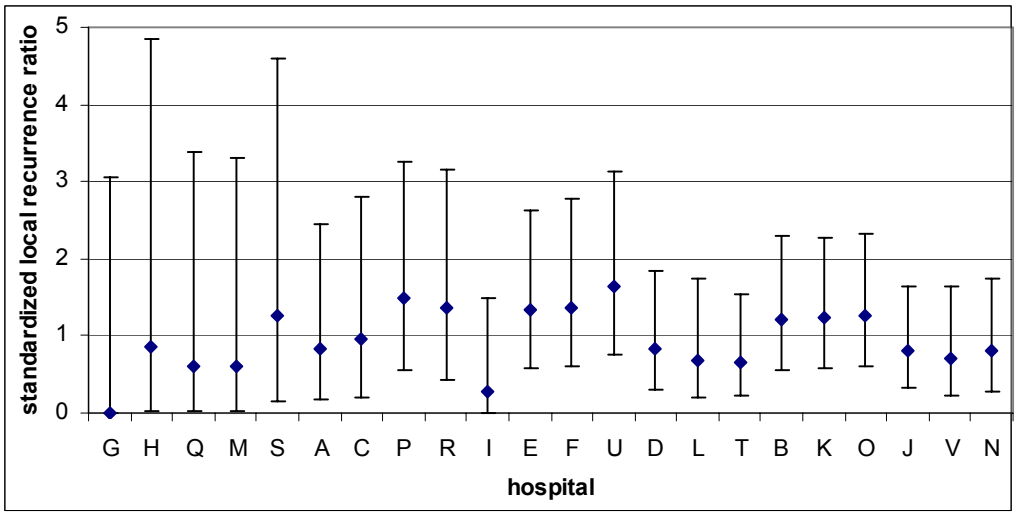

Figure 2. Stage standardized local recurrence ratio after cystectomy for bladder cancer in Greater Amsterdam, 1988-1997 (hospitals are sorted according to the number of cystectomies; bars represent 95% confidence intervals; reference=1 for all hospitals combined)

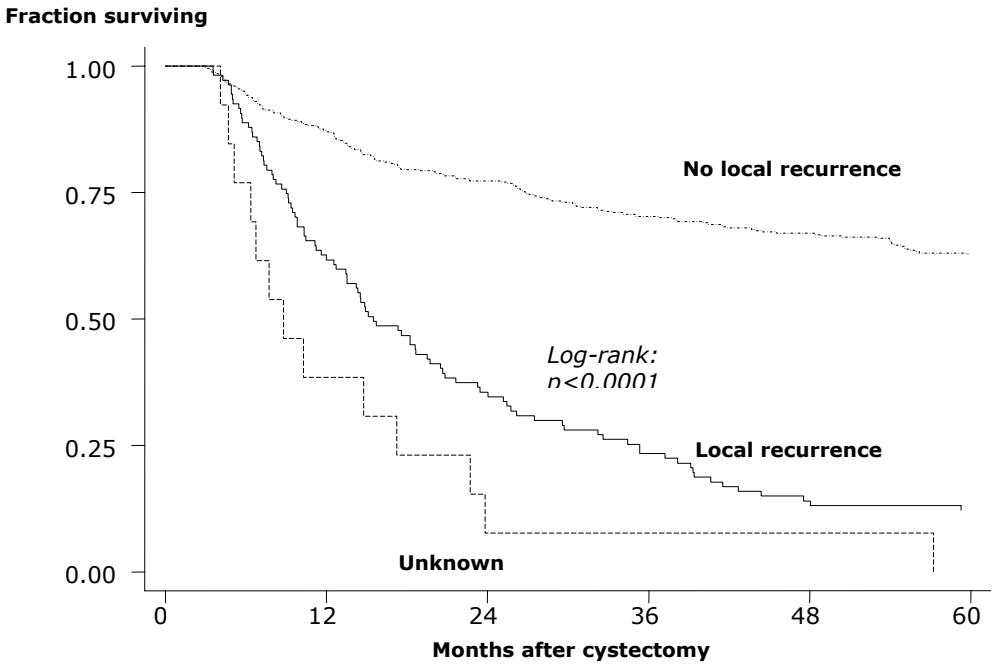

Figure 3. Crude survival after cystectomy for bladder cancer in Greater Amsterdam, 1988-1997 (excluding cases dying within 3 months after cystectomy)

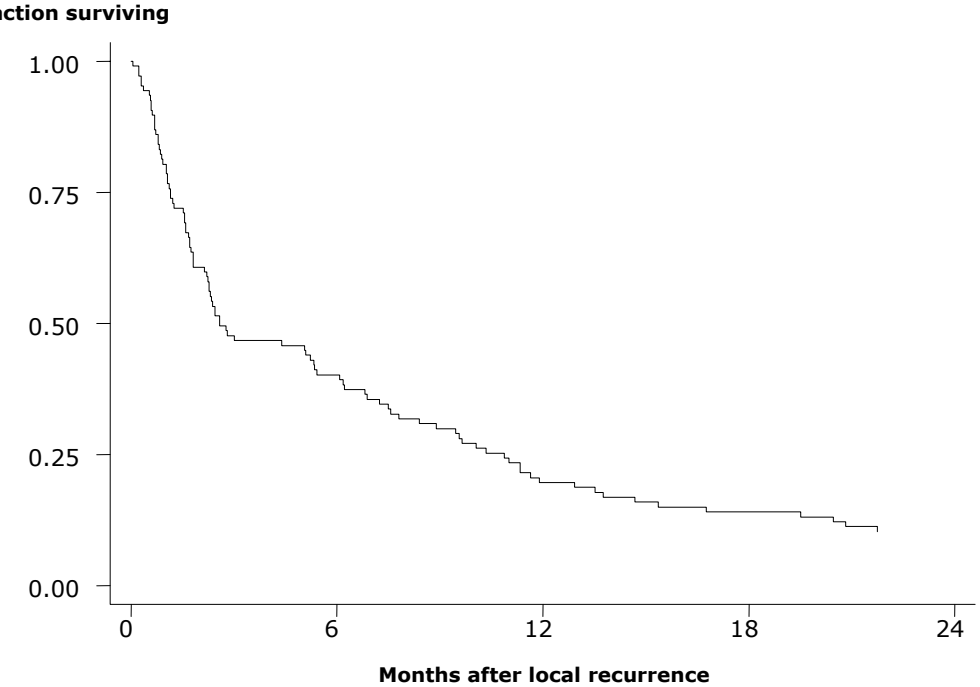

Figure 4. Crude survival according to after local recurrence following cystectomy for bladder cancer in Greater Amsterdam, 1988-1997

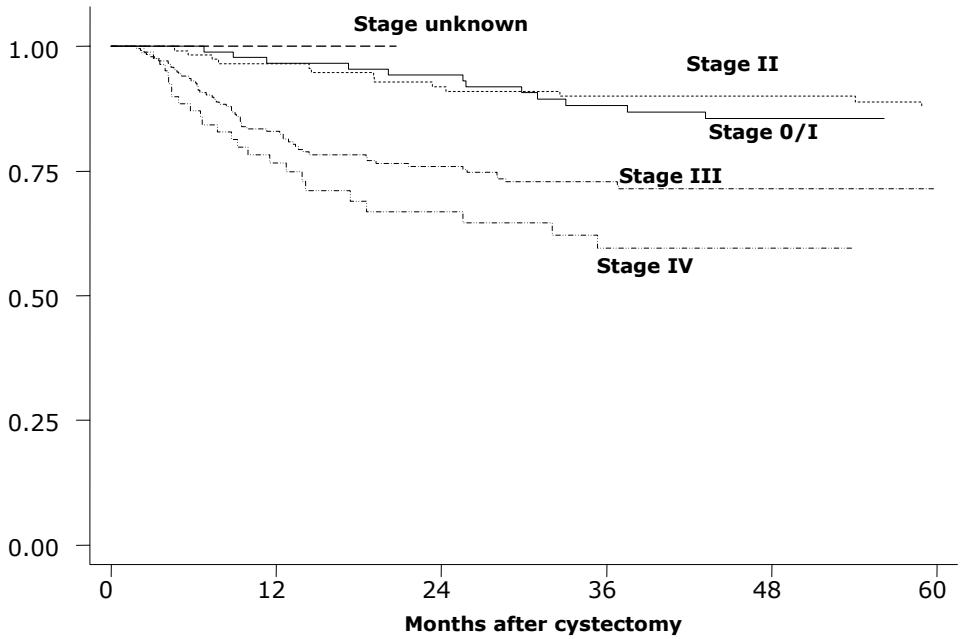

Figure 5. Local recurrence free survival according to pathological stage after cystectomy for bladder cancer in Greater Amsterdam, 1988-1997. Log-rank test: stage III versus stage 0-II: p<0.0001; stage IV versus stage 0-II: p<0.0001; stage III versus stage IV: p=0.07

Local recurrence free survival decreased with increasing stage (figure 5). There was little difference between the lower stages (stage 0-II). However, in stage III (log-rank versus stage 0-II: p<0.0001) and stage IV (log-rank versus stage 0-II: p<0.0001) the risk of local recurrence was higher than in lower stages.

Table 5. Relative survival (%) after cystectomy of bladder cancer patients in Greater Amsterdam, 1988-1997

*pTNM- stage**	Number of cases	years after diagnosis (95% confidence interval)		
		1	5	10
0 / I	96	91 (82-96)	81 (68-92)	78 (59-95)
II	123	92 (84-96)	81 (70-89)	69 (54-82)
III	261	67 (61-73)	44 (37-51)	25 (17-35)
IV	91	60 (49-70)	23 (14-34)	22 (12-33)
Total**	577	76 (72-79)	55 (50-60)	44 (37-50)

* stage grouping according to the 5th edition of the TNM Classification [8], but T4 classifies as stage IV
** Including 6 cases with unknown stage

The stage-specific RSR of patients who underwent a cystectomy (table 5) was higher than for the total group of bladder cancer patients, which comprises all treatments (table 3), with the exception of superficial bladder cancer. For stage II, the 5-year RSR

was 81% for cystectomy patients (pTNM), compared to 44% for all patients combined (cTNM). For stage III, these rates were 44% and 28%, respectively.

DISCUSSION

In this study we evaluated survival and treatment outcomes of patients with bladder cancer. The five-year RSR of patients diagnosed with bladder cancer between 1988-2001 was 75%.
Survival after five years for patients with non-invasive papillary bladder cancer equals survival in the general population (RSR 99%). Between five and ten years after diagnosis survival figures decreased (10-year RSR 92%), but this should be interpreted with caution. These patients are at higher risk to develop invasive bladder cancer than the general population and other factors (e.g. smoking with associated co-morbidity) may also be of importance.
According to the EUROCARE-study on survival of cancer patients in Europe, survival of bladder cancer patients in the Netherlands is among the highest in Europe.[11] The EUROCARE-study reports equally high rates for Germany, Austria, Spain and Sweden. In the EUROCARE-study no data are available on stage distribution, so it is unknown whether this result is due to a more favorable stage distribution or to other factors.
In the USA, the reported bladder cancer survival rates from the SEER-Program are higher than in Europe.[12] Five-year relative survival rates from the SEER-Program for 1990-1999 are 97%, 65%, 56% and 22% for stage I, II, III and IV, respectively, compared to 82%, 44%, 28% and 9% in our study. Although the lower survival in our study may be influenced by differences in staging procedures between the USA and the Netherlands, differences in treatment practices may also have influenced the results. Of all patients who initially presented with clinical stage II-III bladder cancer only 30% underwent a cystectomy. Of the patients <75 years old (probably appropriate candidates) only 44% underwent cystectomy. These percentages are remarkably low in view of the consensus in the Netherlands that cystectomy is the preferred treatment for stage II-III bladder cancer. In our study, survival of patients with stage II-III bladder cancer who underwent a cystectomy was much higher than for all patients combined, but comparison between these patient groups is biased by factors such as age, co-morbidity, and physician's preference. Development of local recurrence in patients undergoing cystectomy has been reported at rates from 7% to 25%.[4-7] Sengelov already demonstrated that intensified examination resulted in more sites of metastases,[13] and local recurrence rates are probably under-reported, as the finding of distant metastases decreases the need for intensified local follow up when local recurrences are asymptomatic. After cystectomy, the tumor recurred locally in one out of five patients in our study, so our results are not among the most favorable when compared to other studies. This might be related to the fact that many other studies were performed in oncological centers, while our study comprised a large number of community hospitals in addition to three oncological centers. No statistically significant difference in SLRR between the various hospitals, nor a relation between the number of cystectomies per hospital and the SLRR could be demonstrated. The LRR in the oncological centers combined was lower, but the difference was not statistically significant. However, the annual number of cystectomies by hospital was rather

low in all hospitals. For oncological centers this was due to the exclusion of referred patients from outside the CCCA region. In recent years, a tendency towards centralization of cystectomies has occurred in our region and future studies should demonstrate whether this has improved the results.
Stage and grade are known prognostic indicators for local failure.[14,15] In contrast to what we expected, no significant difference was found between LRRs after a R0-dissection (no residual tumor after cystectomy) and R1-dissection (microscopic residual tumor). This might be explained by the higher death rates shortly after resection for patients with residual microscopic disease. These patients might not have lived long enough to develop clinical detectable local recurrences. In other series, margin status was a predictor for local recurrence, although no distinction between microscopic or macroscopic residual tumor was made.[16] Furthermore, the use of peri-operative chemotherapy might be of influence. In the time period of our study however, peri-operative chemotherapy was not standard practice. Consequently, only 17 patients underwent this multimodality treatment. This small number does not enable separate analysis and conclusions.
Patients who recur locally usually do so within the first 2 years after treatment, which is consistent with our findings[7,14,17,18].
Differences in LRRs may be influenced by differences in definition. Mostly, local recurrence is defined as bladder cancer recurrence in the soft tissue within the true pelvis, while tumor outside the pelvis is considered as distant metastases. Some authors, however, define a combination of both local and distant recurrence as distant recurrence only, as patient outcome appears to be dictated by concomitant systemic metastases.[17,19] Urethral or upper tract recurrences are sometimes considered as a local recurrence also. However, they represent a different biological process of recurrence, and both treatment and prognosis differ greatly from true pelvic recurrences.[20]
The aggressive natural behavior of local recurrences after cystectomy results in poor prognosis in many series,[14,18] and our data confirm this experience. No data were available about the therapy following local recurrences, but the final outcome of patients with a local recurrence appears to be poor, regardless of treatment. Despite the availability of chemotherapeutic regimens long-term survival is achieved in less than 10% of these patients.[17,18]

CONCLUSIONS

The five-year RSR of all patients combined was 75%, which is slightly better than European figures, but the stage-specific rates are worse than American figures.
Of all patients with stage II-III bladder cancer, only 30% underwent cystectomy. Cystectomy patients experienced a relatively high stage-specific survival. After cystectomy, a local recurrence occurred in one out of five patients, and prognosis for these patients is poor. We found no difference in the LRR between the various hospitals.

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DISCUSSION

In this thesis, a number of descriptive, etiological and prognostic studies are presented which were performed with the population-based cancer registry of the Comprehensive Cancer Centre Amsterdam. The migrant studies show that the cancer risk of migrants from non-western countries differs considerably from the risk of persons who were born in the Netherlands. On the other hand, as is shown in the environmental studies, the influence of air pollution due to air and road traffic on the overall cancer risk seems to be limited. The prognostic studies show that stage is the most important factor to determine survival and that considerable improvement in the prognosis of cancer patients has been achieved for a number of cancers. Not only was this improvement achieved by earlier diagnosis, but also by improved treatment regimens.
The studies in this thesis illustrate the multiple uses of a population-based cancer registry. In this chapter, the results of the studies in the different areas will be put into perspective. In the last section of this chapter prospects for further use of the cancer registry will be discussed.

INTERNATIONAL VARIATION IN CANCER INCIDENCE AND EFFECT OF MIGRATION

Worldwide there are large variations in cancer incidence.[1,2] In general, cancer incidence is much higher in developed countries than in developing countries. However, certain cancer types, such as liver cancer or cervical cancer, are more common in developing countries. There are two main reasons for the worldwide variation in cancer incidence: differences in exposure to environmental and lifestyle factors, such as smoking, diet, radiation, viruses, sexual behaviour, physical activity, etc. and differences in the genetic susceptibility of individuals. Although the risk of cancer for individuals with increased genetic susceptibility may also be influenced by environmental and lifestyle factors, susceptibility for the presently known cancer genes generally increases the life-time risk for a certain cancer much more than any known exposure to environmental or lifestyle factors. For example, cigarette smoking increases the relative risk to die from lung cancer more than 20 times,[3] but nevertheless only a minority of tobacco smokers develop lung cancer[¶],[4] whereas the lifetime risk to develop cancer for carriers of breast cancer genes (BRCA) may be as high as 60-80 percent.[5,6] Probably, there are also (still undiscovered) genes which cause more subtle excess cancer risks.
During the last decades, more and more genes predisposing for cancer have been discovered. Based on present knowledge, the strong susceptibility genes are still thought to be responsible for only a small proportion of cancer cases (5-8%), because the prevalence of these genes in the population is rather low.[7] Migrant studies have contributed to this knowledge. As during migration no change in the genetic composition of a population occurs, changes in cancer incidence after migration are most likely due to environmental and lifestyle factors. For example, studies of Asian migrants to the United States of America have shown that the cancer incidence of the migrant

[¶] In a recent review, it has been estimated that every other smoker will be killed by tobacco. Apart from lung cancer tobacco may cause a large variety of other cancers, including cancer of the oral cavity, pharynx, larynx, oesophagus, pancreas, urinary bladder and renal pelvis, nasal cavities and paranasal sinuses, stomach, liver, kidney (renal cell carcinoma), uterine cervix and myeloid leukaemia. Besides, tobacco increases coronary artery disease, cerebrovascular disease, and atherosclerotic peripheral vascular disease. Because of competing mortality, only a minority of the tobacco smokers will die of lung cancer.

population (Asians) gradually approaches the incidence of the native population (white Americans) within two generations, with incidence of the first generation closest to the incidence in the country of origin and the incidence of the second generation closest to the incidence of the native population.[8,9] In our study among women with residency in Northwest-Netherlands (chapter 2.2), we found that the standardised incidence ratio (SIR) for breast cancer was statistically significantly reduced for women born in Surinam (0.56), Turkey (0.29) and Morocco (0.22). For women from the latter two countries, the SIR was considerably higher in women below the age of 50 (Turkey 0.35; Morocco 0.33) in comparison to women of 50 years or older (Turkey 0.22; Morocco 0.10). Although our data all relate to the first generation, a change of the breast cancer risk in migrants is already observed for women below the age of 50. These women experience a breast cancer risk which is intermediate to the breast cancer risk of older migrants and women born in the Netherlands.

The low breast cancer risk in women born in Turkey and Morocco can probably be attributed to differences in risk factors for breast cancer in comparison to native women, especially in relation to reproduction. Compared to women of Dutch descent, women born in Turkey and Morocco have more children and have their first child at an earlier age. Due to the fact that these women came to the Netherlands as partners of (male) migrant workers, the percentage of unmarried women without children is negligible. The higher breast cancer risk in younger women (below the age of 50) born in Morocco or Turkey, when compared to older women, is probably caused by a change in risk factors in younger women, such as lower parity. As a further change in risk factors (lower parity, increase of age at first child birth) is already observed in second generation migrants,[10] a further change of the breast cancer risk towards the risk in native women seems plausible for second generation migrants in the Netherlands.

Another migrant study (chapter 2.1) revealed that the incidence of cervical cancer among women in North-Holland was significantly higher than the incidence for the nation as a whole (SIR 1.2; 95% CI 1.1-1.2). [11] In particular, the incidence of cervical cancer for women living in Amsterdam (SIR 1.5; 95% CI 1.4-1.6), and for women born in Morocco (SIR 2.1; 95% CI 1.4-3.1) or Surinam (SIR 1.5; 95%CI 1.1-2.0) was much higher. Comparison of the incidence rates for migrant women in North-Holland with the rates in their country of origin revealed that the rates in North-Holland were intermediate to the rate in the country of origin and the rate for native women in the Netherlands. Consequently, a further downward change of the cervical cancer risk in second generation migrants seems likely. Cervical cancer screening might contribute to an acceleration of the decrease in cervical cancer risk of first and second generation migrants.

Therefore, the data on cancer risk among migrants in the Netherlands are not only of epidemiological interest, but they are also relevant from a perspective of public health. As screening programmes are available in the Netherlands both for cervical and for breast cancer, knowledge of the relative risk of subpopulations is essential. Participation of migrant women in these two screening programmes is relatively low, especially the participation of older women from Turkey and Morocco in the breast cancer screening programme is very low. Our study of breast cancer screening attendance (chapter 2.3) showed an overall (age adjusted) attendance of 76 percent for women aged 50-69. Attendance was significantly lower for women born in non-western-

countries (Surinam 59%, Turkey 44%, Morocco 37%) and for native women with residence in Amsterdam (68%). Referral and detection rates for women from non-western countries were 5.1 and 2.2 per 1000 screened women, respectively, compared to 8.8 and 4.0 for women born in the Netherlands ($p<0.05$). As migrant women from non-western countries have a very low breast cancer risk, a passive attitude of the screening organisation with regard to the low participation is justified. On the other hand, efforts should be made to increase the low participation of migrant women in the cervical cancer screening, as the risk of cervical cancer for these women is relatively high.

In the Netherlands, migrant studies are hampered by the unavailability of data on ethnic descent. However, for all Dutch residents the country of birth and the country of birth of the parents are available in the municipal population registers. Since 1995, these data are also available electronically and, potentially, facilitate the study of cancer in migrants, because annual age- and sex-specific population data of first and second generation migrants are available. Unfortunately, in the cancer registry only incomplete information on the country of birth of cancer patients is available, due to incomplete information in the hospitals. Second generation migrants cannot be identified in the cancer registry at all, because information on the country of birth of the parents is lacking. Consequently, for migrant studies extra efforts have to be made to complete the available cancer registry data with regard to the country of birth of cancer patients. For the studies in this thesis, we could use information from the breast cancer screening organisation, as most women who participate in the breast cancer screening had agreed to record linkage with the cancer registry. As many women with breast or cervical cancer are referred to another hospital for (part of) the treatment, we could also use the available information in those hospitals. For males, we could not use these sources and the proportion of registered males with unknown country of birth is higher than for females.

In other European countries, with the exception of Sweden, only few migrant studies were performed, because, like in the Netherlands, only limited information on the migrant status is available in cancer registries. In Sweden, the nationwide Swedish Family-Cancer Database enabled numerous migrant studies, both in first- and second generation migrants. A study among first-generation migrants revealed that among individual cancer sites and immigrant countries, 110 comparisons were significant, 62 showing a decreased risk compared to Swedes and 48 an increased risk.[12] Most of the differences between the rates in immigrants and Swedes could be ascribed to the variation of cancer incidence in the countries of origin. The high lung cancer risk (SIR 2.4) among Dutch males in Sweden is noteworthy. Breast cancer incidence was at or below the Swedish level for all immigrant groups. A study among second-generation migrants and comparison with the results among first-generation migrants suggests that the first two decades of life are important in setting the pattern for cancer development in subsequent life.[13] Birth in Sweden sets the Swedish pattern for cancer incidence, irrespective of the nationality of descent, while entering Sweden in the 20s is already too late to influence the environmentally imprinted programme for the cancer occurrence.

In Saarland, Germany, Razum *et al* successfully tried to identify Turks with a name-based algorithm.[14] However, distinction of first and second generation is not possible when using a name-based algorithm and also the size of the total Turkish population

may be difficult to determine. In the Dutch situation, the total size of the "Turkish-named" population cannot be determined anymore, because many Turks changed their nationality and census data of the number of people who consider themselves as Turkish are not available in the Netherlands, since the last census was held in 1971.
In a study by Bouchardy *et al*, the cancer mortality among North African migrants in France was studied.[15] Although this study offers useful information concerning cancers for which mortality is relatively high, the value of this study is limited for cancers such as testicular cancer, which have a good prognosis. Generally, a low cancer mortality (including mortality due to breast cancer) was observed in North African migrants in comparison to local-born, with the exception of mortality due to cancer of the naso-pharynx and gallbladder. Mortality due to cervical cancer was increased in Moroccan women, but not in other North African women.
The excellent information regarding country of birth and country of birth of the parents as available in the municipal population registers in the Netherlands is a worthwhile source of data for future research among migrants in the Netherlands. However, this data source can only be exploited by linkage to the cancer registry. Unfortunately, privacy regulations hamper such linkage under the present circumstances.

ENVIRONMENTAL STUDIES

The environmental studies in this thesis (chapter 3) show that a population-based cancer registry is a useful tool for studies which investigate the cancer risk of a population with residence in certain well-described geographical entities. In the first study, we estimated the cancer incidence during 1988-2000 in residents of the area surrounding Schiphol. We defined an exposed study area based on aircraft noise contours and 4-digit postal code areas. The second study examined the association between cancer incidence in 1989-97 in Amsterdam and residential traffic intensity. For this study, we linked data on the daily traffic intensity for individual addresses along the main roads of Amsterdam with the population-based regional cancer registry. Information on smoking habits was derived from a smoking survey. In both studies, the overall cancer incidence was not increased, but certain cancer types were less common than expected, while the incidence rates of other cancers were increased. In particular, the increased incidence of haematological malignancies in the Schiphol area was remarkable.
The cancer registry can be relatively easily used for environmental studies, with the additional advantages that it is virtually complete and offers an unselected study population[16]. Yet, there are also several limitations regarding the use of the cancer registry in environmental studies. Firstly, the geographical entity of study and the available exposure data may not coincide with the 4-digit postal code as available in the cancer registry. For example, a study at street-level is not possible with the available cancer registry data and for the study of residential traffic density and cancer incidence in Amsterdam (chapter 3.2), record linkage with the population register of Amsterdam was necessary to obtain the required detailed address information.
Secondly, in the cancer registry the only geographical information that is available relates to the date of diagnosis of cancer. As people may have moved from and to the study area before they were diagnosed with cancer, a proportion of the observed can-

cers is misclassified. This proportion will be larger if mobility in a certain area is higher or if the period of study extends to a prolonged time period. The latter is often necessary to acquire a sufficiently large number of cancer cases. On the other hand, migration *after* the diagnosis is not relevant in a registry-based study. The problem of misclassification could be solved if historical address and exposure data prior to the diagnosis of cancer were available. For the study of residential traffic density and cancer risk in Amsterdam, historical address data were made available by the population register of Amsterdam and they will be used in a future study.
Thirdly and most importantly, no information is available in the cancer registry about confounding factors such as smoking habits, occupation, socio-economic status, alcohol use, diet, sexual behaviour, etc. Consequently, an observed difference in cancer incidence in the study area in comparison to the reference population, such as the increased incidence of haematological malignancies in the Schiphol area, is difficult to interpret. Especially the interpretation of the observed incidence of cancers of the respiratory tract, which may be caused by air pollution,[17,18] as well as by smoking,[19] is difficult in the absence of information on smoking habits of the study population.
Finally, the (un)availability of measurement data regarding relevant environmental exposures may greatly influence the outcome and interpretation of an environmental study. In this respect, there are large differences between the two studies in chapter 3. Although we did not use actual measurements of air pollution in the study of residential traffic density and cancer risk in Amsterdam, the relation between road traffic intensity and air pollution is well-known and detailed measurements of road traffic intensity were available for this study. However, in the study of cancer incidence in the Schiphol area, which was initiated because of serious health concerns of the surrounding population, the available data on air quality did not enable us to define a study area. The noise contours that were used instead, are in fact only a weak surrogate for air pollution. Therefore, the results of the Schiphol study are more difficult to interpret than the results of the study of residential traffic density and cancer risk in Amsterdam.
Because of the inherent limitations of a registry-based environmental study, the finding of an increased cancer incidence in such a study should be followed by a subsequent study in which much more detailed information is available on risk factors, for example a case-control study. On the other hand, if no increased cancer incidence is observed in a population with an allegedly increased cancer risk, a registry-based study is a powerful instrument to refute the alleged increase of cancer risk.
Finally, the registry-based study as a tool for environmental studies would increase its power if there were more possibilities for linkage with other data sources containing information on potential confounding factors, such as socioeconomic status, occupation or smoking habits. Privacy regulations are among the issues which limit the possibilities for such linkage.

PROGNOSTIC STUDIES

Information on the prognosis of cancer patients is important for both patients and their clinicians. Although ample survival data are available from many different studies, only few studies reported on population-based stage-specific survival. The studies in

chapter 4 show that stage is a major prognostic factor for the survival of patients with epithelial cancers and skin melanoma (chapter 4.1). The same result was observed for patients with carcinoid tumours (chapter 4.2). Therefore, the availability of site- and stage-specific survival data from the Amsterdam Cancer Registry is a major step forward. For non-epithelial cancers such as sarcomas, neuro-epithelial tumours and haematological malignancies, stage is of less relevance for the prognosis, which is primarily determined by the morphological type and grade of malignancy of the tumour.[20,21,22] The prognosis of a cancer patient is also influenced by a variety of other factors, such as treatment and co-morbidity.[23,24]

In 1989-2001, stage-specific 5-year relative survival rates (RSR) ranged from close to 100% for stage I carcinoma of the salivary glands, thyroid, colon/rectum, skin, breast, female genital organs, prostate and urethra to 1% or less for stage IV carcinoma of the oesophagus, stomach, liver, gallbladder, pancreas and lung (chapter 4.1). Between 1989-1991 and 1999-2001, we observed an increase of the stage-specific RSR for carcinoma of colon/rectum (stages II-IV), lung (stages I-II), breast (stages I-III) and prostate (stages II-IV). We also observed an increase in survival of metastatic carcinoid tumours between 1980-1991 and 1992-1997 (chapter 4.2), a decrease in the risk of dying of patients with cervical cancer during 1988-1997 (chapter 4.3), but no change in survival of bladder cancer patients during 1988-2001 (chapter 4.4).

Because near complete stage information is available for all relevant sites, we were able to demonstrate that improved survival over time was not merely an effect of changes over time in the stage distribution of newly diagnosed cancer cases. Moreover, because treatment data are available in the cancer registry, we were also able to observe an effect of changes in treatment regimens on stage-specific survival. Although these effects are mostly known already from clinical trials or hospital-based studies, a major drawback of clinical trials and single centre studies is that they only include selected patients, often with a relatively favourable prognosis. Consequently, the results of these studies cannot always be extended to all cancer patients. On the other hand, the results of a cancer-registry based (population-based) survival analysis are based on all cancer patients and thus reflect the results for all cancer patients combined. In interpreting our population-based results, it should be taken into account that individual patients who participate in clinical trials or are treated in specialised cancer hospitals where many hospital studies are performed, may have a more favourable prognosis.

A major drawback of our survival data is that the cause of death is lacking. Consequently, disease-specific survival could not be calculated. Although the relative survival (the ratio between observed and expected survival) is close to the disease-specific survival, the expected survival is calculated with life tables for the general population which include deaths due to cancer. If deaths due to cancer would be excluded from the general life tables, the expected survival would be slightly higher and relative survival slightly lower. As for most cancer sites mortality due to the cancer site concerned only accounts for a small fraction of the total mortality, the effect on the calculated relative survival is very small. The effect is largest for lung cancer in males (in 2001, 9.4% of all deaths in males were due to lung cancer), as well as for all cancer sites combined (in 2001, 30% of all deaths in males were due to cancer, compared to 24% in females). Nevertheless, we estimate that the overestimation of the 5-year relative

survival is less than 0.5% for lung cancer in males, approximately 3% in males for all sites combined and approximately 1% in females for all sites combined.
Although the cause of death is available at Statistics Netherlands for all deceased Dutch residents, this information has not been easily accessible for research due to the very strict privacy regulations of Statistics Netherlands. However, a recent adaptation of the law might broaden the possibilities to use this information source in the future.

PROSPECTS FOR FURTHER USE OF A POPULATION-BASED CANCER REGISTRY: QUALITY INDICATORS IN ONCOLOGICAL PRACTICE

In recent years, there has been a tendency in Dutch society towards an increased transparency of publicly financed institutions as far as their results are concerned. This applies to schools, universities, hospitals, etc. However, the results of hospitals are not easily determined. The outcome of a patient's treatment is influenced by a variety of factors, many of which are not related to the medical treatment as such. For example, patient behaviour (e.g. adherence to prescribed medication), co-morbidity, socio-economic status or genetic susceptibility may influence the outcome of a medical treatment. Besides, depending on specific treatments available, specialised hospitals may attract specific subpopulations of cancer patients, for example patients with a poor prognosis who seek specialised treatment, or, on the other hand, patients with a high socio-economic status and a relatively favourable prognosis, who prefer treatment in a specialised hospital. The variation of the patient populations between hospitals may seriously hamper the comparison of treatment outcome of various hospitals and, consequently, the interpretation of possible differences in treatment outcome has to be performed with the utmost care.
Although the regional cancer registry collects data in all hospitals, the data can only be used to map certain aspects of the treatment and its outcome of cancer patients.

Hospital volume

The determination of the number of patients with a specific cancer type that is treated in each hospital in a certain time period can easily be determined by the cancer registry. This number is hardly subject to confounding factors and can be compared to the number that is generally considered necessary to establish and maintain experience in the diagnosis and/or treatment of that type of cancer. The relation between volume and treatment outcome has been the subject of many studies.[25] Although hospital volume has been found to be associated with treatment outcome in a number of studies, for example in studies regarding surgical treatment of oesophageal and pancreatic cancer[26] or treatment of metastatic non-seminomatous germ cell cancer,[27] no association was found in other studies.[28,29] Also in our study of bladder cancer (chapter 4.4), a relation between hospital volume and the risk of local recurrence was not found. Consequently, for each separate cancer, the pros and cons of centralisation of cancer treatment have to be carefully considered.

Adherence to guidelines

For many cancers, guidelines for diagnostic and treatment procedures have been or are being developed in the Netherlands, as a result of a cooperation of the Association of Comprehensive Cancer Centres, the Dutch Institute for Healthcare Improvement and the Order of Medical Specialists.[30] The cancer registry can be used to evaluate the adherence to these guidelines at the hospital-level. For example, the percentage of breast cancer patients that received adjuvant treatment according to the guidelines can be determined. If supplementary data have to be collected, this is preferably done for a limited number of cases for a limited time period in a so-called 'documentation project'.

Recurrence

Although recurrence (local, regional and/or distant) is not (yet) part of the standard item set that is collected by the Amsterdam Cancer Registry, recurrence has been collected additionally for colorectal cancers diagnosed 1988-1991, rectal cancers diagnosed 1998-2000 and bladder cancers diagnosed 1988-1997 (chapter 4.4). The study of bladder cancer shows that local recurrence occurred in one out of five patients and that survival after recurrence was poor. Therefore, the monitoring of the occurrence of (local) recurrence is a good indicator for oncological practice. Unfortunately, the collection of recurrence is very time consuming and cannot (yet) be performed on routine basis.
The recurrence rate can be calculated for all hospitals combined and compared to the rate as known from other studies in the international literature. Moreover, the rate can be calculated for each separate hospital and compared between hospitals. However, the comparison between hospitals is often hampered by the relatively low absolute number of recurrences, which results in large confidence intervals, and the variation in the patient populations of the different hospitals.
An option for future research in the field of recurrence and adherence to guidelines would be a case-control study in which adherence to diagnostic and treatment guidelines in cases with a recurrence would be compared to adherence to the guidelines in controls who did not develop a recurrence while having similar follow-up time. Such a design is efficient since data collection is only needed for a sample of all patients. It requires, however, that the notification of recurrence is performed efficiently, for example by means of the national pathology database ('PALGA') or the hospital discharge registry.

Survival

Like the recurrence rate, survival can be calculated for each individual hospital. However, while recurrence is always cancer-related, overall (and relative) survival is also influenced by mortality due to other causes than cancer. Therefore, in the comparison between hospitals the use of disease-specific survival is preferred. Even if disease-specific survival is available a comparison between hospitals should be made with care, as in certain hospitals patients with a worse/better than average prognosis may be more common than in other hospitals. This may be due to differences in age, sex, comorbidity, socio-economic status, presence of family cancer clinic or other (partially

unknown) determinants. Of course, it is possible to adjust the results for a number of co-variates (age, sex and stage, at the least), but since not all co-variates are available, residual confounding may play a role and, consequently, the results still have to be interpreted with caution.

Occurrence of second or subsequent cancers

As the population-based cancer registry records all primary tumours occurring in a patient, it is an ideal tool for the monitoring of the occurrence of second or subsequent cancers. Most of the second or subsequent cancers share etiological factors with the first primary, such as smoking-related cancers (e.g. lung cancer and head & neck cancer), or occur in one patient by coincidence (e.g. prostate cancer and skin cancer). However, a (relatively small) proportion of second or subsequent cancers are a (late) effect of the treatment of the first primary. Over the past decades, treatment-related second cancers have been demonstrated in, for example, patients treated for Hodgkin lymphoma, testicular cancer and breast cancer.[31,32,33,34] In the future, the population-based cancer registry can make an important contribution to the elucidation of presently unknown associations between various cancers and the influence of treatment factors. As with the years the number of registered patients with prolonged follow-up continues to increase, the power of the cancer registry to detect such associations will also increase. An advantage of the NCR, as compared to registries in many other countries, is that treatment data are available. In general, further, more detailed, studies will be necessary to elucidate the nature of the observed associations.

Other indicators

There are many other possible indicators of oncological care, for example psychosocial indicators (patient satisfaction, adequate information, etc), indicators of the hospital process (waiting lists, time interval between first hospital visit and diagnosis or between diagnosis and start of treatment, etc), morbidity or adverse effects of the treatment. For such indicators a population-based cancer registry is a less useful instrument, since either the registration process is too slow, patient contact is essential, or the collection of the data would be too time-consuming. However, if certain indicators were to be collected for a limited number of patients and for a limited time period, the infrastructure of the cancer registry could be used for the collection of the requested information in the framework of a 'documentation project'.

Due to their limitations and the difficult interpretation of differences between hospitals, recurrence or survival rates are not suitable for distribution among the general public. These rates should rather be used as internal information for the hospital or as information for the medical professionals concerned, e.g. for the Tumour Working Groups. By contrast, there are few drawbacks with regard to the publication of hospital volumes for specific cancers, waiting lists or duration of the diagnostic process.
As in the past, the cancer registry will continue to submit the available information to the hospitals and their medical specialists. It is up to them to separate this information into data for internal and external use.

The announced introduction of a personal identification number ('Burger Service Nummer') in all public services (including the health sector), when included in the cancer registry, will increase the efficiency of the follow-up procedures of the cancer registry substantially. Because such a number enables anonymous record linkage with other registries (preferably through a trusted third party in order to protect the privacy of those registered), it will also offer new perspectives for future etiological studies with the cancer registry, including second generation migrant studies.

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6

SUMMARY

Since 1989, the Netherlands has a nation-wide population-based cancer registry, which is composed of nine regional registries. The Amsterdam Cancer Registry (ACR) is one of these regional registries, which started its activities in 1984 and reached region-wide coverage in 1988. All hospitals in North-Holland and Flevoland (twenty in 2005) participate in the ACR. The population size of the region amounted to 2.9 million on January 1st 2004, including 14 percent first generation migrants and 12 percent second generation migrants.

The number of registered cancers in the region of the ACR increased from 9 500 in 1988 to 12 000 in 2002 (+26%), but the age-standardised incidence rate per 100 000 persons only slightly increased (from 377 in 1988 to 389 in 2002). The male/female ratio decreased from 1.4 in 1988 to 1.2 in 2002.
Cancers of the breast, lung, colon & rectum and prostate account for 50 percent of all cancers. In 1988, lung cancer was the most common cancer, but since 1991, breast cancer is the most common cancer. Other common cancer sites are the bladder, stomach, head & neck, bone marrow and lymphatic tissues. Of all registered invasive cancers in 1988 7 percent concerned a second or subsequent cancer. This percentage increased to more than 10 percent in 2002.
The number of cancer deaths has been rather stable during 1988-2002, but the age-standardised mortality rate per 100 000 persons decreased by 16 percent, mainly due to a decrease in lung cancer mortality in males, but also mortality due to stomach cancer, prostate cancer, breast cancer and ovarian cancer decreased.
Cancer prevalence in North-Holland/Flevoland numbered 61 100 persons in 2003, mostly breast cancer (16 300), skin cancer (7 700), colorectal cancer (7 500) and prostate cancer (6 600). Cancer prevalence comprises a large variety of patients, including patients in the diagnostic phase or in the primary treatment phase, cured patients and patients in the terminal phase, with different needs for care in each phase.
Follow-up of vital status has been performed for all incident cases diagnosed 1988-2001, which enabled the calculation of cancer survival rates. During 1988-2001, survival slightly improved for all cancer sites combined. This is due to improved survival of some common cancers (breast cancer, colorectal cancer, prostate cancer) as well as changes in cancer incidence: the proportion of several cancers with poor survival (lung cancer, stomach cancer) has decreased between 1988 and 2001, while the proportion of cancers with a relatively favourable prognosis (breast cancer, prostate cancer, skin cancer) has increased.

Apart from the use of a cancer registry for the calculation of cancer incidence rates, there are numerous possibilities for research with population-based cancer registries, ranging from descriptive epidemiological studies and health care planning to aetiological and clinical research. In this thesis, the various uses of a population-based cancer registry are illustrated by migrant studies (chapter 2), etiologic studies of the association between environmental factors and the occurrence of cancer (chapter 3) and research on prognosis and survival of cancer patients (chapter 4).

The first migrant study (chapter 2.1) is a descriptive epidemiological study and describes the incidence of cervical cancer in North-Holland according to country of birth.

The number of cases of cervical cancer in North-Holland for the period 1988-1998, by country of birth, was determined on the basis of data available from the ACR. Based on data from the Netherlands Cancer Registry, a comparison was made between the observed and the expected number of cases by area of residence (i.e., Amsterdam versus the rest of North-Holland) and by country of birth. In the period 1988-1998, the incidence of cervical cancer among women living in North-Holland was significantly higher than the national rate (standardised incidence ratio [SIR] 1.2; 95% confidence interval [CI] 1.1-1.2). In particular, the incidence of cervical cancer for women living in Amsterdam (SIR 1.5, CI 1.4-1.6), and for women born in Morocco (SIR 2.1, CI 1.4-3.1) or Surinam (SIR 1.5, CI 1.1-2.0) was much higher. With the exception of Turkish women, the incidence rate among migrant women in the North-Holland was below the rate in their country of origin. The percentage of patients with higher stages (TNM-stages II-IV) did not differ between women born in the Netherlands and those born abroad. In conclusion, the incidence of cervical cancer during the period 1988-1998 was significantly higher for women living in Amsterdam and for women born in Morocco or Surinam than that for the Netherlands as a whole. No significant difference in stage of disease at diagnosis was observed between women born in the Netherlands versus those born abroad.

The second migrant study (chapter 2.2) is also a descriptive epidemiological study and describes the incidence of breast cancer in North-Holland and The Hague according to country of birth. In 1988-1998, the SIR for breast cancer was statistically significantly reduced for women born in Surinam (0.56), Turkey (0.29) and Morocco (0.22). For women from the latter two countries, the SIR was considerably higher below the age of 50 (Turkey 0.35; Morocco 0.33) in comparison to older women (Turkey 0.22; Morocco 0.10). In women born in Indonesia, the opposite was found (<50 years 0.83; 50 years or older 1.03). The proportion of women with advanced stages (III and IV) did not differ significantly between migrants and women born in the Netherlands. Although the risk of breast cancer among women resident in the Netherlands but born in Surinam, Turkey and Morocco is still close to the risk in their country of origin, the higher risk in younger women compared to older women from Turkey and Morocco indicates that a change in the breast cancer risk profile (e.g. lower parity) towards the risk profile of native women is already occurring in first generation migrants.

For the third migrant study (chapter 2.3) we did not use cancer registry data, but this study was based on data from the regional breast cancer screening organisation, in order to determine breast cancer screening results according to country of birth. Overall (age adjusted) attendance of the breast cancer screening was 76 percent for women aged 50-69. Attendance was significantly lower for women born in non-western-countries (Surinam 59%, Turkey 44%, Morocco 37%) and also for women with residence in Amsterdam in general (68%). Referral, detection and interval carcinoma rates for women from non-western countries were 5.1, 2.2 and 1.2 per 1000 screened women, respectively, compared to 8.8, 4.0 and 2.2 for women born in the Netherlands ($p<0.05$). The positive predictive value was 45 percent for women born in the Netherlands and western countries and 43 percent for women born in non-western countries. Although women born in non-western countries attend breast cancer screening less frequently than women born in the Netherlands, they also have a low

detection rate and a low interval carcinoma rate. The latter findings justify a passive attitude towards the low attendance.

The first study in chapter 3 is an example of an ecological (correlation) study (chapter 3.1). The reason for this study was that Amsterdam Airport Schiphol has long been a major source of complaints about aircraft noise, safety risks and noise- and pollution-related adverse health effects, including cancer. We estimated the cancer incidence during 1988-2003 in residents of the area surrounding Schiphol. As the available exposure data on air pollution did not enable us to define a study area, we based the study area on aircraft noise contours and 4-digit postal code areas. In residents of the study area 13 207 cancer cases were diagnosed, which was close to the expected number, using national incidence rates as a reference (SIR 1.02). When examining the individual cancer sites, for most sites no increased or decreased risks were observed. The incidence of cancer of the respiratory system was statistically significantly decreased (SIR 0.94, CI 0.90-0.99), due to the low rate in males (SIR 0.89). We also found a statistically significantly increased incidence of haematological malignancies (SIR 1.12, CI 1.05-1.19), mainly due to high rates for non-Hodgkin lymphoma (SIR 1.22, CI 1.12-1.33) and acute lymphocytic leukaemia (SIR 1.34, CI 0.95-1.83). In the core zone of the study area, where aircraft noise levels were highest, cancer incidence was slightly higher than in the remaining ring zone (rate ratio of the core zone compared to the ring zone 1.05, CI 1.01-1.10). This was caused by a relatively high incidence of cancer of the respiratory system, prostate and female genital organs in the core zone in comparison to the ring zone.
In this study no individual data regarding the exposure to aircraft-related air pollution were available. Besides, neither information on migration to and from the study area, nor on confounding factors such as smoking habits, occupation, socio-economic status, alcohol use, diet, sexual behaviour, etc. was available. Consequently, the interpretation of the results of this ecological study is difficult. Therefore, although the overall cancer incidence was not increased, further research is necessary to elucidate the cause of the relatively high incidence of haematological malignancies.
The second environmental study (chapter 3.2) differs from the first one with regard to the availability of individual exposure data in the second study. In this study, we examined the association between residential traffic intensity and cancer incidence in 1989-97 in Amsterdam. We linked data on the daily traffic intensity for individual addresses along the main roads with the population-based regional cancer registry. Information on smoking habits was derived from a smoking survey. During 1989-1997, 27 157 cancer cases were diagnosed in Amsterdam residents. Using the age group- and sex-specific cancer incidence in the population not residing along the main roads as a reference, the SIR of the population residing along the main roads was 1.03, (3 384 cases), while the 95% confidence interval included unity (1.00–1.07). For most cancer sites the SIR was close to 1, except for gastrointestinal cancer in males (SIR 1.16, CI 1.04-1.28), cancer of the respiratory tract in females (SIR 1.13, CI 0.97-1.31) and haematological malignancies in adult females (SIR 1.23, CI 1.04-1.44). Five cases of acute lymphocytic leukaemia were diagnosed in children along the main roads (SIR 2.5, CI 0.8-5.9). Smoking habits did not differ between residents along the main roads and those living along other roads. Although we found no clear evidence for an asso-

ciation between residence along main roads and the incidence of cancer in adults, we cannot exclude an association with haematological malignancies in females and children.

Chapter 4 includes a number of prognostic studies which made use of the follow-up data of the cancer registry. While stage is the most important factor for determining cancer survival, population-based survival data according to stage are rarely presented. In chapter 4.1 we present such data for a large population diagnosed with cancer in the area covered by the Amsterdam Cancer Registry in 1989-2001 (n=108251). Cases were grouped according to the TNM-Classification. For all sites, a strong influence of stage at diagnosis on survival was observed. The stage-specific 5-year relative survival rate (RSR) ranged from close to 100% for stage I carcinoma of the salivary glands, thyroid, colon/rectum, skin, breast, female genitals, prostate and urethra to ≤ 1% for stage IV carcinoma of the oesophagus, stomach, liver, gallbladder, pancreas and lung. Between 1989-1991 and 1999-2001, we observed an increase of the stage-specific RSR for carcinoma of colon/rectum (stages II-IV), lung (stages I-II), breast (stages I-III) and prostate (stages II-IV). Analysis of trends in stage distribution and treatment practices support the assumption that changes in diagnostic (breast, prostate) and staging procedures (lung), new/improved surgical techniques (rectum, prostate) and adjuvant treatment (breast, colon) are likely to have contributed to the observed increase in the stage-specific RSRs.
In chapter 4.2, we studied the incidence and survival of carcinoid tumours. Carcinoid tumours are rare malignant neuro-endocrine tumours. In 1992, octreotide was introduced in the Netherlands as a palliative treatment for the carcinoid syndrome in metastatic carcinoid disease. The aims of this descriptive study were to evaluate epidemiological data (age-, sex-, site- and stage-specific incidence) and the impact of octreotide on survival in metastatic carcinoid disease. As carcinoid tumours are rare, we used incidence data from the Netherlands Cancer Registry. Survival data from two registries (the ACR and the Eindhoven Cancer Registry) were available for 619 patients, diagnosed between 1980 and 1997. Between 1989-1996, the incidence of carcinoid tumours in the Netherlands was 1.95/100 000 population (2 391 patients). Under the age of 50 years a significant female predominance was observed. Under the age of 35 years, appendiceal carcinoid was the most frequently diagnosed primary site. The occurrence of distant metastases at diagnosis for appendiceal and lung carcinoids was 1.6% and 5.5%, respectively, compared to 40% in carcinoids at other primary sites. The 5-year RSR was 72% for all carcinoids combined, and ranged from 93% for localised disease, 74% for regional extension, to 19% in case of distant metastasis. Multivariate analysis revealed that older age and higher stage were independent predictors of worse survival, while appendix localisation predicted better survival. In a sub-group analysis of metastatic disease, year of diagnosis after 1992 was the only predictor of better survival (p=0.012). The female predominance found under the age of 50 years suggests hormonal influence. Improved survival in metastatic carcinoid disease might be related to the use of octreotide.
In order to evaluate the effect of population-based cervical cancer screening, which restarted after a reorganisation in 1995, on the occurrence of cervical cancer in the region of the ACR, we investigated the incidence and survival of cervical cancer in

chapter 4.3. In this descriptive study, we observed a significant decrease in the age-standardised incidence rate of squamous cell carcinoma from 9.2/100 000 women in 1988 to 5.9/100 000 in 2000 ($p<0.001$). The incidence rate of adenocarcinomas remained stable (incidence rate 1.6 in 1988 and 2000). After adjustment for age, stage and lymph node involvement, the relative risk of death was 1.6 (CI 1.3-2.1) times higher for patients with adenocarcinomas than for patients with squamous cell carcinoma. The decreased survival was related to histological type, as the effect remained significant after correction for confounding factors. Over time, the prognosis of women with squamous cell carcinoma improved significantly. No significant change was observed for women diagnosed with adenocarcinoma. These results suggest that the screening programme in The Netherlands as executed in the region of the ACR is associated with a decreased incidence and increased survival of patients with squamous cell carcinoma, but fails to detect (pre)malignant lesions of adenocarcinoma. Since more than 92% of adenocarcinomas and its precursors contain high-risk HPV, adding HPV testing to cytologic screening might improve the present screening programme in detecting adenocarcinoma and its precursor lesions.
In the fourth study of chapter 4, we determined retrospectively, in a population-based study, the survival of patients with bladder cancer and the local recurrence rate (LRR) after cystectomy (chapter 4.4). All bladder cancer cases diagnosed between 1988 and 2001 were selected for this study from the ACR. For all patients who underwent a cystectomy between 1988 and 1997 in 18 participating hospitals, information on local recurrence and vital status was collected from the medical records. Five-year relative survival for all bladder cancer cases combined (n=8 321) was 75%. For clinical stage 0-a this was 99%, decreasing to 85% for stage 0-is and 82% for stage I, and to 44%, 28% and 9% for stages II, III and IV, respectively. Five-year relative survival after cystectomy was 81%, 44% and 23% for stages II, III and IV bladder cancer, respectively. The LRR after cystectomy (n=566) was 19% for all cases and institutions combined. The LRR increased with higher pT-stages and reached 11%, 23% and 31% for stage II, III and IV respectively, and was slightly lower in oncological centres (18%) than in community hospitals (20%) (not significant). Survival was higher than the European average, but below the figure for the United States. Only one in three stage II-III patients was treated with cystectomy. A relatively high stage-specific survival was experienced after cystectomy, in spite of a local recurrence in 1 out of 5 patients.

In chapter 5 (the general discussion) the results of the various studies are discussed. Also, prospects for further use of a population-based cancer registry are presented. Apart from studies as already presented in this thesis, there are possibilities to use the cancer registry as a tool for the measurement of quality in oncological practice, for example with respect to adherence to guidelines, recurrence, disease-specific survival (for the whole region or by hospital) or other indicators (e.g. waiting lists, morbidity or adverse effects of the treatment, co-morbidity). If supplementary data have to be collected, this should preferably be done for a limited number of cases for a limited time period in a so-called 'documentation project'. Finally, as the population-based cancer registry records all primary tumours occurring in a patient, it is an ideal tool for the monitoring of the occurrence of second or subsequent primary cancers. In the future, the population-based cancer registry may make an important contribution to the eluci-

dation of presently unknown associations between various cancers and the influence of treatment factors. As with the years the number of registered patients with long follow-up continues to increase, the power of the cancer registry to detect such associations will also increase.

The announced introduction of a personal identification number ('Burger Service Nummer') in all public services (including the health sector), when included in the cancer registry, will increase the efficiency of the follow-up procedures of the cancer registry substantially. Because such a number enables anonymous record linkage with other registries (preferably through a trusted third party in order to protect the privacy of those registered), it will also offer new perspectives for future etiological studies with the cancer registry, including second generation migrant studies.

SAMENVATTING

Sinds 1989 beschikt Nederland over een landelijk dekkende ('population-based') kankerregistratie die is samengesteld uit negen regionale registraties. De kankerregistratie van het Integraal Kankercentrum Amsterdam (IKA) is een van deze negen regionale registraties. De IKA-kankerregistratie begon in 1984 en is regiodekkend vanaf 1988. Alle ziekenhuizen in Noord-Holland en Flevoland (twintig in 2005) nemen deel aan de IKA-kankerregistratie. De regio had een inwonertal van 2,9 miljoen op 1 januari 2004, waaronder veertien procent eerste generatie allochtonen en twaalf procent tweede generatie allochtonen.

Het aantal geregistreerde gevallen van kanker in de regio van het IKA nam toe van 9500 in 1988 tot 12 000 in 2002 (+26%), maar het naar leeftijd en geslacht gestandaardiseerde incidentiecijfer per 100 000 personen vertoonde slechts een kleine stijging (van 377 in 1988 naar 389 in 2002). De verhouding tussen het incidentiecijfer bij mannen en dat bij vrouwen daalde van 1,4 in 1988 naar 1,2 in 2002.

Kanker van de borst, long, darm en prostaat vormen ongeveer de helft van alle kankers. In 1988 kwam longkanker nog het meeste voor, maar sinds 1991 is borstkanker de meest voorkomende vorm van kanker. Andere veel voorkomende vormen van kanker zijn blaaskanker, maagkanker, kanker van hoofd & hals en kanker van de lymfatische en bloedvormende weefsels. Van alle in 1988 geregistreerde maligniteiten was 7 procent een tweede of latere maligniteit. In 2002 was dit aandeel gestegen tot 10 procent.

Het aantal sterfgevallen ten gevolge van kanker veranderde niet veel in de periode 1988-2002, maar het naar leeftijd en geslacht gestandaardiseerde sterftecijfer per 100000 personen daalde met 16 procent, vooral door een daling van de sterfte ten gevolge van longkanker bij mannen. Er deed zich echter ook een daling voor van de sterfte ten gevolge van maagkanker, prostaatkanker, borstkanker en eierstokkanker.

Het totale aantal (ex-)kankerpatiënten ('prevalentie') in Noord-Holland/Flevoland bedroeg in 2003 61 100 personen, waaronder 16 300 met borstkanker, 7 700 met huidkanker, 7 500 met darmkanker en 6 600 met prostaatkanker. Kankerprevalentie omvat een zeer diverse groep personen, zoals patiënten bij wie onderzoek wordt gedaan om de ziekte in kaart te brengen, patiënten die voor hun ziekte behandelingen ondergaan, patiënten in de terminale fase en personen die genezen zijn. In elke fase van het ziekteproces is er andere zorgbehoefte.

Van alle patiënten bij wie voor het eerst kanker was vastgesteld in 1988-2001 is er vervolgonderzoek gedaan naar de vitale status (al dan niet overleden). Op basis van dit gegeven konden overlevingskansen worden berekend. In de periode 1988-2001 verbeterden de overlevingskansen licht voor alle vormen van kanker samen. Dit komt enerzijds door hogere overlevingskansen van enkele veel voorkomende vormen van kanker (borstkanker, darmkanker, prostaatkanker), anderzijds door veranderingen in incidentie: het aandeel van enkele vormen van kanker met een slechte prognose (longkanker, maagkanker) daalde tussen 1988 en 2001, ten gunste van het aandeel van enkele vormen van kanker met een gunstige prognose (borstkanker, prostaatkanker, huidkanker).

Behalve dat de kankerregistratie gebruikt kan worden voor berekening van incidentiecijfers, zijn er talloze mogelijkheden voor onderzoek met 'population-based' kankerregistraties, variërend van beschrijvende epidemiologische studies en planning van gezondheidsvoorzieningen tot etiologisch (gericht op de oorzaak van ziekten) en klinisch onderzoek. In dit proefschrift wordt het gebruik van de kankerregistratie geïllustreerd met behulp van migrantenstudies (hoofdstuk 2), etiologische studies naar het verband tussen omgevingsfactoren en het optreden van kanker (hoofdstuk 3) en onderzoek naar de overlevingskansen van kankerpatiënten (hoofdstuk 4).

De eerste migrantenstudie (hoofdstuk 2.1) beschrijft de incidentie van baarmoederhalskanker in Noord-Holland naar land van geboorte. Het aantal gevallen van baarmoederhalskanker in Noord-Holland gedurende de periode 1988-1998, per geboorteland, werd vastgesteld op basis van gegevens uit de IKA-kankerregistratie. Met behulp van gegevens van de Nederlandse Kankerregistratie werd een verwacht aantal gevallen van baarmoederhalskanker berekend per geboorteland en per woonregio (Amsterdam versus de rest van Noord-Holland) en vergeleken met het waargenomen aantal. In de onderzochte periode bleek de incidentie van baarmoederhalskanker in Noord-Holland significant hoger (gestandaardiseerde incidentie ratio [SIR[§§]] 1,2; 95% betrouwbaarheidsinterval [BI] 1,1-1,2) dan het landelijke gemiddelde. Vooral bij vrouwen woonachtig in Amsterdam (SIR 1,5, BI 1,4-1,6), en bij vrouwen geboren in Marokko (SIR 2,1, BI 1,4-3,1) en Suriname (SIR 1,5, BI 1,1-2,0) was de incidentie hoog. Het incidentiecijfer bij allochtone vrouwen in Noord-Holland was lager dan in hun land van herkomst, met uitzondering van Turkse vrouwen. Het aandeel van patiënten bij wie de ziekte in een vergevorderd stadium (TNM-stadium II-IV) was vastgesteld, verschilde niet tussen autochtone en allochtone vrouwen. Concluderend was de incidentie van baarmoederhalskanker significant verhoogd bij vrouwen woonachtig in Amsterdam en bij vrouwen geboren in Marokko of Suriname. Er werd tussen autochtone en allochtone vrouwen geen significant verschil gevonden in het stadium bij diagnose.

De tweede migrantenstudie (hoofdstuk 2.2) beschrijft de incidentie van borstkanker naar land van geboorte bij vrouwen woonachtig in Noord-Holland en Den Haag. In 1988-1998 bleek de SIR significant verlaagd voor vrouwen die waren geboren in Suriname (0,56), Turkije (0,29) en Marokko (0,22). Bij vrouwen afkomstig uit de laatste twee landen was de SIR minder laag onder de 50 jaar (Turkije 0,35; Marokko 0,33) dan boven de 50 jaar (Turkije 0,22; Marokko 0,10). Bij vrouwen die in Indonesië geboren waren was het juist andersom (<50 jaar 0,83; 50 jaar of ouder 1,03). Het aandeel van vrouwen bij wie de ziekte in een vergevorderd stadium (III en IV) werd vastgesteld verschilde niet significant tussen allochtone en autochtone vrouwen. Hoewel het risico op borstkanker bij allochtone vrouwen in Nederland nog weinig verschilt van het risico op borstkanker bij vrouwen in het land van herkomst, is het hogere risico van jongere vrouwen in vergelijking met oudere vrouwen een aanwijzing dat een verandering van het risicoprofiel voor borstkanker (bijv. een lager gemiddeld kindertal) naar het risicoprofiel van autochtone vrouwen al gaande is in eerste generatie allochtonen.

Voor de derde migrantenstudie (hoofdstuk 2.3) is geen gebruik gemaakt van gegevens van de kankerregistratie, maar van gegevens van de regionale organisatie voor borstkankerscreening. Deze gegevens zijn gebruikt om de screeningsresultaten per land van

[§§] Een SIR van 1 geeft aan dat in de onderzochte groep net zoveel kanker voorkomt als in de groep waarmee wordt vergeleken. Bij SIR>1 komt er meer kanker voor en bij SIR<1 juist minder.

geboorte te bepalen. De totale (naar leeftijdsgroep gestandaardiseerde) opkomst bij het bevolkingsonderzoek bedroeg 76 procent voor vrouwen van 50-69 jaar. De opkomst was veel lager bij vrouwen geboren in niet-westerse landen (Suriname 59%, Turkije 44%, Marokko 37%). Ook in Amsterdam was de opkomst relatief laag (68 procent voor alle geboortelanden samen). Het verwijscijfer, het detectiecijfer en het intervalcarcinoomcijfer voor vrouwen geboren in niet-westerse landen was respectievelijk 5,1, 2,2 en 1,2 per 1000 gescreende vrouwen, tegen 8,8, 4,0 en 2,2 voor in Nederland geboren vrouwen ($p<0,05$). De positief voorspellende waarde was 45 procent voor vrouwen geboren in Nederland en westerse landen, tegen 43 procent voor vrouwen geboren in niet-westerse landen. Hoewel vrouwen geboren in niet-westerse landen minder deelnemen aan het bevolkingsonderzoek op borstkanker dan vrouwen die in Nederland zijn geboren, is ook het detectiecijfer en het intervalcarcinoomcijfer laag. Deze laatste bevinding rechtvaardigt een passieve houding ten opzichte van de lage opkomst.

De eerste studie in hoofdstuk 3 is een voorbeeld van een ecologische (correlatie-) studie (hoofdstuk 3.1). Schiphol is al lange tijd een bron van klachten over geluidsoverlast, veiligheidsrisico's en aan geluidsoverlast en luchtvervuiling gerelateerde gezondheidschade, waaronder kanker. Deze klachten waren de aanleiding om te onderzoeken hoeveel kanker zich in de periode 1988-2003 voordeed bij inwoners van de regio rond Schiphol. Omdat op basis van de beschikbare meetgegevens over de luchtvervuiling in de regio geen studiegebied kon worden gedefinieerd, hebben we een gebiedsindeling gemaakt op basis van geluidscontouren van vliegtuiglawaai en 4-cijferige postcodegebieden. Bij inwoners van het studiegebied werden in totaal 13 207 gevallen van kanker vastgesteld, hetgeen vrijwel gelijk was aan het aantal dat kon worden verwacht op basis van landelijke cijfers (SIR 1,02). Bij nadere beschouwing van de verschillende vormen van kanker werd voor de meeste kankersoorten geen verhoogd of verlaagd risico waargenomen. Kanker van de luchtwegen kwam statistisch significant minder voor dan verwacht (SIR 0,94, BI 0,90-0,99) doordat het vooral bij mannen minder vaak voorkwam (SIR 0,89). Kanker van bloedvormend en lymfatisch weefsel kwam juist vaker voor dan verwacht (SIR 1,12, BI 1,05-1,19), vooral doordat non-hodgkinlymfoom (SIR 1,22, BI 1,12-1,33) en acute lymfoblastenleukemie (SIR 1,34, BI 0,95-1,83) relatief veel voorkwamen. In de kernzone van het studiegebied - het gebied met de hoogste geluidbelasting – was de incidentie van kanker iets hoger dan in het omringende gebied (verhouding tussen kernzone en omringende gebied: 1,05, BI 1,01-1,10). Dit werd veroorzaakt doordat in de kernzone kanker van de luchtwegen, van de prostaat en van de vrouwelijke geslachtsorganen in verhouding meer voorkwamen dan in het omringende gebied.

In deze studie waren geen gegevens beschikbaar met betrekking tot de individuele blootstelling aan luchtvaart-gerelateerde luchtvervuiling. Ook ontbrak informatie over migratie van en naar het onderzoeksgebied of over andere factoren die de resultaten kunnen beïnvloeden, zoals rookgewoonten, beroep, sociaal-economische status, alcoholgebruik, voeding, seksueel gedrag, enz. Hierdoor is de interpretatie van de resultaten van deze ecologische studie moeilijk. Daarom is verder onderzoek nodig om de oorzaak van de relatief hoge incidentie van kanker van de bloedvormende en lymfatische weefsels te achterhalen, hoewel de totale kankerincidentie niet verhoogd was.

Het tweede onderzoek naar de invloed van het milieu op het voorkomen van kanker (hoofdstuk 3.2) verschilt van de het eerste onderzoek, omdat in de tweede studie gegevens met betrekking tot de individuele blootstelling beschikbaar waren. In deze studie hebben we de relatie onderzocht tussen de verkeersintensiteit en het voorkomen van kanker in de periode 1989-1997 in Amsterdam. Gegevens over de verkeersintensiteit van individuele adressen langs het hoofdverkeersnet zijn gekoppeld aan de regionale kankerregistratie. Gegevens over rookgewoonten zijn verkregen uit een enquête. In de periode 1989-1997 werden in totaal 27 157 gevallen van kanker vastgesteld bij inwoners van Amsterdam. Gebruikmakend van de leeftijdsgroep- en geslachtspecifieke kankerincidentie bij de bevolking die *niet* langs het hoofdverkeersnet woonde als referentie, was de SIR van de bevolking die *wel* langs het hoofdverkeersnet woonde 1,03 (3 384 gevallen van kanker), waarbij het 95% betrouwbaarheidsinterval liep tot 1 (1,00-1,07). Voor de meeste vormen van kanker was de SIR dicht bij 1, behalve voor kanker van de spijsverteringsorganen in mannen (SIR 1,16, BI 1,04-1,28), kanker van de luchtwegen in vrouwen (SIR 1,13, BI 0,97-1,31) en kanker van bloedvormend en lymfatisch weefsel in volwassen vrouwen (SIR 1,23, BI 1,04-1,44). Er werden vijf gevallen van acute lymfoblastenleukemie vastgesteld bij kinderen die woonden langs het hoofdverkeersnet (SIR 2,5, BI 0,8-5,9). De rookgewoonten verschilden niet tussen de bevolking die langs het hoofdverkeersnet woonde en de bevolking die in andere straten woonde. Hoewel we geen duidelijk bewijs hebben gevonden voor een relatie tussen wonen langs het hoofdverkeersnet en het voorkomen van kanker bij volwassenen, kunnen we niet uitsluiten dat er een relatie bestaat met kanker van bloedvormend en lymfatisch weefsel bij vrouwen en kinderen.
Hoofdstuk 4 bevat een aantal studies over de prognose van kankerpatiënten, waarvoor gebruik gemaakt is van vervolggegevens van de kankerregistratie.
Hoewel het stadium van de ziekte de belangrijkste factor is die de overleving bepaalt van kankerpatiënten, worden overlevingscijfers naar stadium zelden gepubliceerd. In hoofdstuk 4.1 worden deze gegevens gepresenteerd voor een grote groep kankerpatienten woonachtig in de regio van de IKA-kankerregistratie bij wie in de periode 1989-2001 kanker is vastgesteld (n=108 251). Alle gevallen werden gerubriceerd naar soort kanker en het stadium op basis van de TNM-classificatie. Voor alle soorten kanker werd een sterke invloed van het stadium op de overleving waargenomen. Het stadium-specifieke 5-jaarsoverlevingscijfer varieerde van vrijwel 100% voor stadium I (het gunstigste stadium) carcinoom van de speekselklieren, schildklier, darm, huid, borst, vrouwelijke geslachtsorganen en urinebuis tot 1% of minder voor stadium IV (het ongunstigste stadium) carcinoom van de slokdarm, maag, lever, galblaas, alvleesklier en long. Tussen 1989-1991 en 1999-2001 werd een stijging van het stadium-specifieke 5-jaarsoverlevingscijfer waargenomen bij carcinoom van de darm (stadium II-IV), long (stadium I-II), borst (stadium I-III) en prostaat (stadium II-IV). Nadere beschouwing van de trends in stadiumverdeling en behandeling van kankerpatiënten ondersteunt de veronderstelling dat veranderingen in diagnostiek (borst, prostaat), stadiëringsonderzoek (long), nieuwe/verbeterde chirurgische technieken (endeldarm, prostaat) en aanvullende behandelingen (borst, dikke darm) hebben bijgedragen aan de waargenomen verbetering van de stadium-specifieke overlevingscijfers.
In de volgende studie hebben we het voorkomen en de overleving van carcinoïden onderzocht (hoofdstuk 4.2). Carcinoïden zijn zeldzame kwaadaardige neuro-endocriene

tumoren, die hormonen kunnen produceren en daarmee het carcinoïd-syndroom veroorzaken. In 1992 werd octreotide in Nederland geïntroduceerd als een palliatieve behandeling voor patiënten met een carcinoïd-syndroom ten gevolge van een uitgezaaid carcinoïd. Het doel van de studie was het beschrijven van de beschikbare epidemiologische gegevens (naar leeftijd, geslacht, lokalisatie en stadium) van carcinoïden in Nederland (op basis van gegevens van de Nederlandse Kankerregistratie) en het onderzoeken van de invloed van octreotide op de overleving (op basis van de IKA- en IKZ-kankerregistraties). In de periode 1989-1996 werd in totaal bij 2391 personen in Nederland een carcinoïd vastgesteld (1,95 geval per 100000 inwoners). Onder de 50 jaar werd bij vrouwen vaker een carcinoïd gevonden dan bij mannen. De appendix was de meest voorkomende lokalisatie van een carcinoïd bij personen jonger dan 35 jaar. Uitzaaiingen op afstand kwamen weinig voor bij carcinoïden in de appendix (1,6%) en de long (5,5%), maar in 40% van de gevallen bij carcinoïden in andere organen. De relatieve 5-jaarsoverleving bedroeg 72% voor alle carcinoïden samen en varieerde van 93% voor gelokaliseerde ziekte, 74% voor carcinoïden met regionale uitbreiding en 19% in het geval van uitzaaiingen op afstand. In een multivariate analyse bleken hogere leeftijd en hoger stadium onafhankelijke factoren die een slechtere overleving veroorzaken; carcinoïden gelokaliseerd in de appendix veroorzaken juiste een gunstiger overleving. In een analyse met alleen uitgezaaide ziekte bleek dat carcinoïden die na 1992 werden gediagnosticeerd een gunstiger overleving hadden (p=0,012). Het feit dat vrouwen onder 50 jaar vaker carcinoïden hebben dan mannen suggereert dat hormonen invloed hebben op het ontstaan van carcinoïden. De verbeterde overleving na 1992 zou veroorzaakt kunnen zijn door de toepassing van octreotide na 1992.
In 1995 is het bevolkingsonderzoek op baarmoederhalskanker gereorganiseerd. In hoofdstuk 4.3 is, ter evaluatie van het bevolkingsonderzoek, onderzocht hoe de incidentie en overleving van baarmoederhalskanker zich hebben ontwikkeld in de regio van de IKA-kankerregistratie. Er werd een significante daling waargenomen van het naar leeftijd gestandaardiseerde incidentiecijfer van plaveiselcelcarcinoom, de meest voorkomende variant van baarmoederhalskanker (van 9,2 gevallen per 100000 vrouwen in 1988 naar 5,9 in 2000). Het incidentiecijfer van adenocarcinoom van de baarmoederhals veranderde niet (1,6 gevallen per 100000 vrouwen). Na correctie voor leeftijd, stadium en betrokkenheid van lymfklieren in het ziekteproces, bleek dat vrouwen met een adenocarcinoom een hogere sterftekans (relatief risico op sterfte 1,6, BI 1,3-2,1) hebben dan vrouwen met een plaveiselcelcarcinoom van de baarmoederhals. Gedurende de onderzoeksperiode is de prognose van vrouwen met plaveiselcelcarcinoom significant verbeterd, maar een significante verbetering deed zich niet voor bij vrouwen met adenocarcinoom. Deze resultaten suggereren dat het bevolkingsonderzoek op baarmoederhalskanker in Nederland is geassocieerd met een daling van de incidentie en een stijging van de overleving van plaveiselcelcarcinoom, maar dat (voorstadia van) adenocarcinoom onvoldoende wordt opgespoord. Omdat meer dan 92% van de (voorstadia van) adenocarcinomen humaan papillomavirus bevatten, zou het toevoegen van een test op humaan papillomavirus aan de huidige cytologische screening het aantal opgespoorde (voorstadia van) adenocarcinomen kunnen verhogen.
In de vierde studie van hoofdstuk vier (hoofdstuk 4.4) is de overleving van patiënten met blaaskanker onderzocht, alsmede de kans op het terugkomen van de kanker ('lokaal recidief') na operatieve verwijdering van de blaas ('cystectomie'). Alle gevallen

van blaaskanker die vastgesteld werden in de periode 1988-2001 werden geselecteerd uit de IKA-kankerregistratie. Van alle patiënten bij wie de blaas operatief werd verwijderd in de periode 1988-1997, werden aanvullende gegevens (lokaal recidief en eventuele overlijdensdatum) verzameld in 18 deelnemende ziekenhuizen. De relatieve 5-jaarsoverleving bedroeg 75% voor alle gevallen van blaaskanker samen (n=8321). Voor klinisch stadium 0-a bedroeg de overleving 99%, dalend naar 85% voor stadium 0-is en 82% voor stadium I, en tot 44%, 28% en 9% voor respectievelijk stadium II, III en IV. De relatieve 5-jaarsoverleving na cystectomie was 81%, 44% en 23% voor respectievelijk stadium II, III en IV. Na cystectomie (n=566) kwam de blaaskanker terug in 19% van alle gevallen. De blaaskanker kwam vaker terug bij hogere stadia en bereikte waarden van 11%, 23% en 31% voor respectievelijk stadium II, III en IV. Het percentage was iets lager in oncologische centra (18%) dan in algemene ziekenhuizen (20%) (niet significant). De overleving was hoger dan het Europese gemiddelde, maar lager dan in de Verenigde Staten. Slechts een op de drie patiënten met stadium II-III onderging een cystectomie. Na cystectomie werd een relatief hoge stadium-specifieke overleving waargenomen, ondanks het feit dat bij een op de vijf patiënten de ziekte terugkwam.

In hoofdstuk 5 (de discussie) worden de resultaten van de verschillende studies besproken. Ook komen mogelijkheden voor toekomstig onderzoek aan de orde. Behalve studies waarvan in dit proefschrift al voorbeelden zijn opgenomen, zijn er mogelijkheden om de kankerregistratie te gebruiken als instrument om de kwaliteit te meten van de oncologische zorg, bijvoorbeeld met betrekking tot het volgen van richtlijnen, het percentage patiënten waarbij de ziekte terugkomt na een behandeling, ziektespecifieke overleving (voor de gehele regio of per ziekenhuis) of andere indicatoren (bijv. wachtlijsten, bijwerkingen van de behandeling, bijkomende ziekten, enz.). Als voor het beantwoorden van een vraagstelling aanvullende gegevens moeten worden verzameld, moet dit bij voorkeur gebeuren voor een beperkt aantal gevallen van kanker gedurende een beperkte periode in een zogeheten documentatieproject. Tenslotte is een 'population-based' kankerregistratie een ideaal instrument voor onderzoek naar het optreden van tweede tumoren na een eerdere vorm van kanker. In de toekomst kan de kankerregistratie een belangrijke bijdrage leveren aan de opheldering van thans onbekende associaties tussen verschillende vormen van kanker of de invloed van de behandeling. Omdat met het verstrijken der jaren het aantal geregistreerde patiënten met een lange overlevingsduur blijft toenemen, nemen ook de mogelijkheden om met de kankerregistratie dergelijke associaties waar te nemen toe.

Met de invoering van het burgerservicenummer in het publieke domein, waaronder de gezondheidszorg, zal het vervolgen van patiënten in de toekomst veel gemakkelijker worden, indien het gebruik van dit nummer ook aan de kankerregistratie zal worden toegestaan. Omdat het burgerservicenummer anonieme koppelingen (bij voorkeur via een derde partij om de privacy van de geregistreerden te beschermen) mogelijk maakt met andere registraties, opent dit nieuwe perspectieven voor studies met de kankerregistratie, waaronder studies met tweede generatie allochtonen.

DANKWOORD

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Voor de studies in hoofdstuk 4 waren de gegevens die de gemeenten in de provincies Noord-Holland en Flevoland, alsmede het Centraal Bureau voor de Genealogie, hebben verstrekt over overleden personen onontbeerlijk. Jakko Nieuwenhuijzen, Simon Horenblas, Saskia Bulk, Pascal Quaedvlieg, met jullie heb ik een artikel mogen schrijven waarbij gebruik werd gemaakt van follow-up gegevens. Dank voor de prettige samenwerking! Maryska Janssen-Heijnen wil ik danken voor de IKZ-overlevingscijfers die ik heb mogen gebruiken in het onderzoek over carcinoïden.
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CURRICULUM VITAE

Otto Visser werd geboren op 22 juni 1960 te Ridderkerk. Nadat hij in 1978 het diploma Gymnasium B had behaald aan Het Christelijk Lyceum in Dordrecht volgde hij de studie geneeskunde aan de Erasmus Universiteit Rotterdam. Eind 1984 werd het artsexamen met goed gevolg afgelegd. In 1985 heeft hij ziektewetcontroles gedaan voor diverse bedrijfsverenigingen (o.a. het Sociaal Fonds Bouwnijverheid). In 1986 werd hij voor 4 jaar aangesteld als assistent in opleiding bij de afdeling Inwendige Geneeskunde II van de medische faculteit van de Erasmus Universiteit Rotterdam, waar hij onderzoek deed naar diverse vormen van porfyrie. In 1990 trad hij in dienst bij het Integraal Kankercentrum Amsterdam (IKA), eerst als plaatsvervangend hoofd onderzoek & registratie, later als hoofd kankerregistratie. Hij heeft zich bij het IKA onder andere beziggehouden met de kwaliteit van en verslaglegging over de kankerregistratie, zowel op regionaal als landelijk niveau. Zijn inspanningen op het gebied van de follow-up van kankerpatiënten hebben geleid tot deelname van het IKA aan de EUROCARE-studie naar de overleving van kankerpatiënten in Europa, waaraan tot dusver alleen door de kankerregistratie van het IKZ volledig werd meegedaan.